PATHOGENESIS OF TRAUMATIC URÆMIA
A REVISED CONCEPT*

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THE descriptions of fatal cases of severe oliguria among air-raid casualties in the 1939–45 war (Bywaters and Beall 1941, Dunn et al. 1941, Bywaters and Dible 1942) aroused considerable interest in acute renal failure, and within a few years it became recognised as one of the most important disorders affecting the kidneys.

Acute renal failure after injury is now ascribed to renal tubular necrosis (fig. 1a), but this explanation is unsatisfactory because inter alia it cannot account for the non-oliguric form of the uræmia, the composition of the urine —particularly the absence of glycosuria and the low sodium and high potassium content—or the occasional cases without tubular necrosis. There is an alternative explanation, the central theme of which is a persistent and often irreversible fall in the rate of glomerular filtration (figs. 1b and 7).

Oliguric and Nonoliguric Uræmia

The oliguric syndrome has received more attention because it is easily diagnosed and is more dangerous to life, but it is only part of the spectrum of traumatic uræmia.

Nonoliguric uræmia has been described in burns (Sevitt 1956a, 1957), battle casualties (Teschan et al. 1955), following head injury and major surgery (Taylor and Reid 1956), and after other injuries in civil life and incompatible blood-transfusion (Sevitt 1959). It is at least as common as the oliguric form but is likely to be overlooked. The absence of oliguria is explained by a diminished tubular reabsorption of water which is sufficient to balance the reduced amount filtered by the glomeruli (Graber and Sevitt 1959).

Azotæmia is considerable in both forms; the blood-urea level reaches 200-800 mg. per 100 ml. and the plasma-creatinine 5–20 mg. per 100 ml., according to the duration and the excess of post-traumatic protein catabolism. The urea and creatinine clearances fall often to only 5% to 10% of normal, reflecting the low rate of glomerular filtration.

The distinction between oliguric and nonoliguric forms is clinically important because severe persistent oliguria produces the dangers of water retention, hyperkalæmia, hypocalcæmia, and acidosis which need special therapy. The term oliguria is, however, a little arbitrary because there is a considerable range of urine output in different cases, and even at different times, in one patient. Moreover the upper limit of urinary volume in oliguria has been difficult to define; some regard 300 ml. per day as the maximum (Bull et al. 1949), others 400 ml. (Swan and Merrill 1953), others 500 ml. (Lucké 1946, Teschan et al. 1955), and others as much as 1 litre per day (Muirhead and Stirman 1952).

The urine shows the essential post-traumatic pattern of low sodium and chloride and high potassium concentrations, irrespective of the volume passed.

Oliguria is followed by diuresis if the patient survives; and at this stage the urine has been reported to contain large quantities of sodium, potassium, and chloride alleged to result from faulty tubular reabsorption. This explanation is unlikely to be correct because the excess of potassium must result from a high rate of tubular excretion. The negative balance of sodium and chloride is usually the response to previous overloading, so prolonged salt wasting is a myth; the high output of salt is maintained by continued overadministration in the belief that the kidney is unable to conserve salt (Merrill 1955). Both oliguric and nonoliguric cases may show identical patterns of renal tubular necrosis.

Tubular Necrosis and Renal Dysfunction

Although various names emphasising special features have been given to the histological pictures, including "lower-nephron nephrosis" (Lucké 1946), "hæmoglobinuric nephrosis" (Mallory 1947), "glomerulo-tubulo-nephrosis" (Zollinger 1952), and "tubulo-interstitial nephritis" (Brun 1954), necrosis of tubules is said to be characteristic (Oliver et al. 1951, Oliver 1953, Dible 1953) and the picture has been named acute tubular necrosis. This was subdivided into distal tubular and proximal tubular necrosis according to the main site of lesions, whilst distal tubular necrosis was further divided into diffuse and focal kinds according to the histological density (Sevitt 1956a, 1957). Hydropic and hyaline-droplet changes in the proximal tubules are not uncommon, but are not related to tubular necrosis and are probably osmotic and metabolic effects respectively (Graber and Sevitt 1959).

The common finding of tubular necrosis does not establish it as the morphological basis of renal failure since association does not prove causality. The association is often close, but it is not invariable since one can occur without the other (fig. 4). Early changes are often slight or absent (Dible 1953), particularly when there is no excretion of pigment, and this is an important discrepancy in view of the emphasis paid to tubular damage.

* Based on a paper given to the pathology section of the Manchester Medical Society on March 11, 1959.

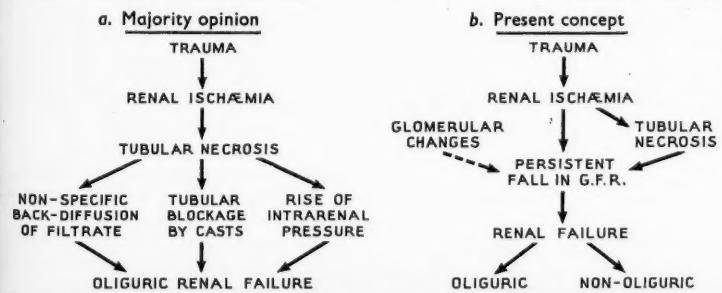

Fig. 1—The essential mechanisms postulated in pathogenesis of traumatic uræmia. a= majority opinion. b=present, revised concept.

RELATION OF TUBULAR NECROSIS TO RENAL DYSFUNCTION IN 64 FATALLY BURNED PATIENTS

Clinical state	Distal tubular necrosis		Proximal tubular necrosis	No tubular necrosis
	Diffuse	Focal		
Severe persistent oliguria ..	13	3	7	..
Severe azotæmia without oliguria	8	2	3	2
Temporary or moderate azotæmia without oliguria ..	2	2	1	1
No azotæmia, no oliguria ..	1	19	..	..

Patients without tubular necrosis and renal dysfunction have been excluded. Numerals refer to numbers of patients.

In the accompanying table the correlation between tubular necrosis and renal function (oliguria and azotæmia as indices) is shown in 64 fatally burned patients.

Of 38 patients with oliguric or nonoliguric uræmia 31 died with diffuse distal tubular necrosis or with proximal tubular necrosis; but in 5 others the distal tubular necrosis was focal, and in 2 it was absent. Of the 6 patients who died after a moderate temporary azotæmia 3 had also extensive proximal or distal tubular necrosis, but in the other 3 tubular damage was focal or absent. Many cases with histological changes died without evidence or suspicion of renal damage, but in most of these the lesions were not extensive; of 20 cases of distal tubular necrosis without azotæmia the histological change was focal in 19.

Other workers have reported discrepancies between renal morphology and function. On the one hand Brun and Munck (1957) found tubular necrosis in only 5 of 33 cases of acute renal failure; whilst, on the other, Mallory (1947) found hæmoglobinuric nephrosis in 19% of fatal battle casualties, and Anderson and Steer (1955) reported renal lesions in as many as 36% of men dying from war wounds after reaching hospital. The latter contrasts with 0·5% of cases of traumatic uræmia among wounded men reaching hospital and 1·6% among major surgical cases in the same battle area (Teschan et al. 1955, Ladd 1955).

Thus tubular necrosis can occur without renal failure, and vice versa. They are commonly associated probably because they have pathogenetic factors in common. Microdissection studies (Oliver et al. 1951, Darmady 1957) have confirmed that many nephrons are normal even when many others are damaged; so when tubular necrosis is present there are two populations of nephrons, damaged and undamaged.

The important conclusion cannot be escaped that tubular necrosis is not the basis of traumatic uræmia, although of course it reduces the number of nephrons capable of function. The kidney reserve is large, however, and more than three-quarters of renal parenchyma has to be removed surgically before a clinical effect is produced.

Tubular Function

Excretion of Electrolytes

After burning and injury the electrolyte composition of the urine quickly changes: either the concentrations of sodium and chloride both fall immediately (1–20 mEq. per litre), or there is a low chloride level with intermittent low sodium phases; the potassium concentration rises acutely up to 100 or even 200 mEq. per litre, followed by a higher than normal level (figs. 2–4). These changes depend on the adrenocortical secretion of aldosterone and are part of the body reaction to " stress " and oligæmia.

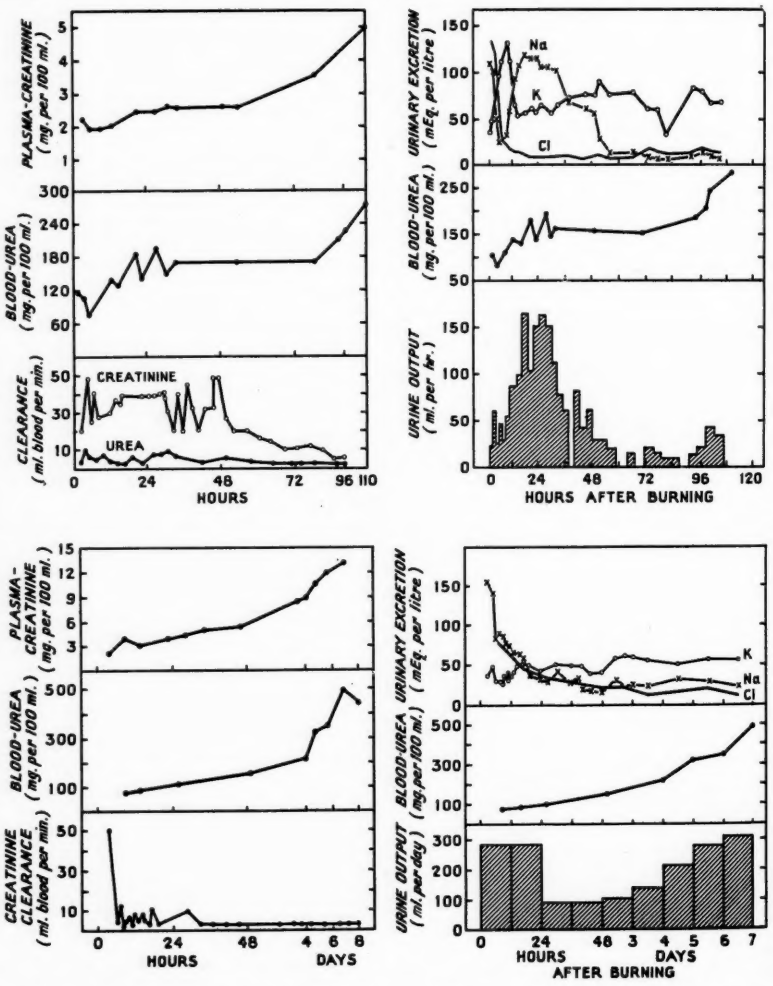

Fig. 2—Serial investigations of two cases with renal failure after extensive burning. The top two figures refer to a patient with nonoliguric uræmia, the bottom two figures to a patient with severe oliguria.

Note (1) the low creatinine clearance (G.F.R.) and developing azotæmia in both patients (left-hand figures); (2) on the right-hand side, the high urinary concentration of potassium, low urinary concentration of chloride, and low concentration of sodium (phasic in top figure) in both cases.

Figs. 2 and 5 are taken from Graber and Sevitt (1959).

Essentially similar patterns are found in oliguric and non-oliguric patients irrespective of the fall in glomerular filtration-rate (G.F.R.) or the presence or absence of azotæmia or tubular necrosis. They reflect tubular hyperactivity because low urinary concentrations of sodium and chloride are due to active tubular reabsorption from the filtrate and high potassium concentrations to active tubular excretion.

Tubular activity is indicated by the high plasma/urine (P/U) ratios for sodium and chloride and high urine/plasma (U/P) ratios for potassium, but reabsorption of sodium is more accurately assessed according to Platt's (1950) formula by calculating the fraction of the sodium filtered by the glomeruli which is excreted in the urine. Values below the normal 2% or so are found (often 0·1–0·5%) and are proof of active tubular

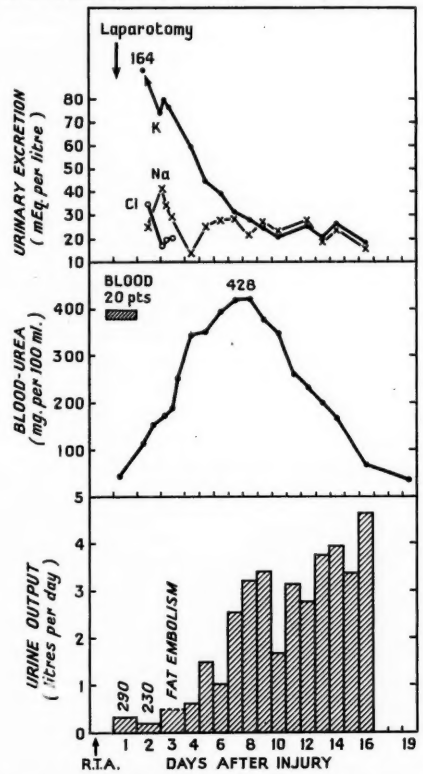

Fig. 3—Severe posttraumatic uræmia with 3–4 days of oliguria and evidence of continued tubular activity.

Note (1) the low urinary concentrations of sodium and chloride, and the high concentration of potassium even during the phase of oliguria; (2) the progressive azotæmia during the early phase of diuresis. The patient survived.

reabsorption (fig. 5). The tubular ability to differentiate between sodium and chloride is often revealed by short phases of high-sodium/low-chloride output during which the urine contains large amounts of bicarbonate. Evidence of tubular hyperactivity may either persist until death supervenes, or recur after the stress of subsequent operation or infection or before the patient succumbs. Tubular necrosis is often found at necropsy; but sometimes it is slight or even absent so function does not necessarily accord with the histological appearances. Ladd (1955) also concluded that tubular reabsorption of sodium was normal, while Taylor (1957) found high P/U ratios for sodium and chloride.

In contrast are the relatively low P/U ratios for sodium and chloride (generally 2–3:1) reported by Bull et al (1950), who

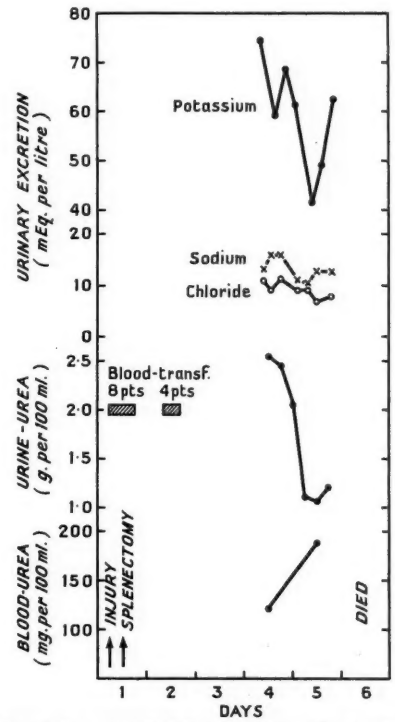

Fig. 4—Uræmia in a severely injured patient. Continued tubular activity is indicated by the high concentration of urinary potassium and low concentrations of urinary sodium and chloride.

The uræmia was at least partly related to the onset of paralytic ileus. Tubular necrosis was not found at necropsy.

concluded that the urine approximated to a plasma filtrate because of impaired tubular activity. Their ratios and those of Brun (1954) varied, however, from case to case, that for chloride ranging from 10 to 1. Few of their cases were post-traumatic; and few, if any, were studied from the time of the incident precipitating the oliguria, when the renal response of the adrenocortical reaction to stress might have been very apparent. Their finding of a high potassium excretion during the early diuretic phase is indicative of tubular hyperactivity, not an inability to conserve potassium since potassium excretion is an active distal tubular process.

In brief, tubular ability to reabsorb sodium and chloride, to excrete potassium, and to differentiate between these ions (and other substances) indicates a high degree of persistent tubular power, and may be in contrast to the degree of tubular necrosis found.

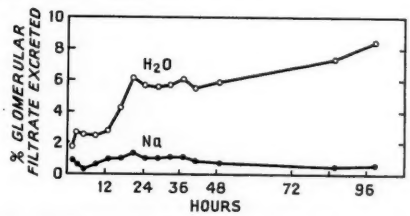

Fig. 5—Percentage excretion in the urine of water and sodium filtered by the glomeruli in a case of acute renal failure after burning.

Note (1) the low excretion of filtered sodium (less than 1%) indicative of active tubular reabsorption; (2) the progressive rise in the fraction of filtered water excreted indicative of diminished tubular reabsorption. 0=time of burning.

Tubular Reabsorption of Water

The tubular reabsorption of water is reduced even though the reabsorption of sodium and chloride is increased. Normally about 1% of the filtered water is excreted as urine, but in patients with severe azotæmia following burning or injury the fraction excreted rises progressively (fig. 5) and may reach 10–15%.

Overall the fraction is inversely related to the G.F.R. and parallels the rising blood-urea level. Water reabsorption is reduced in both nonoliguric and oliguric uræmia. The volume of urine passed depends on the balance between the low G.F.R. and the reduced reabsorption of water; oliguria is absent when the reduced reabsorption balances the reduced filtration, and is present when compensation is inadequate. Reduced reabsorption of water has been attributed to impaired tubular activity (Bull et al. 1950), but then it would be a selective impairment because other absorptive powers seem adequate. It might be an osmotic tubular diuresis related to the rising head of urea in the plasma filtrate, or it might be mediated by inhibition or antagonism of antidiuretic hormone.

Urine Concentration

The urine specific gravity (1010–1016) and osmolarity (350–450 milliosmols per litre) are both relatively low, but not because of tubular dysfunction as has been alleged. The concentration of solutes is lowered by the diminished reabsorption of water from the filtrate, and the low concentration of urea is mainly responsible.

Reabsorption of Glucose

Glycosuria is common after all severe injuries and is related to an acute hyperglycæmic response. It is usually transient even when uræmia develops, but glucose tolerance may be decreased for a time. Bull et al. (1950) agreed that glycosuria was rare in oliguric failure, and, since glucose is reabsorbed by the proximal tubules, found this difficult to explain on the basis of tubular damage. Glycosuria appeared after a loading dose of glucose, and they calculated that the tubular reabsorptive power was impaired. After injury this would be difficult to distinguish from the common decrease in glucose tolerance. If it reflects tubular damage, the effect might be a summation phenomenon reflecting the inactivity of damaged tubules and the activity of normal ones.

Excretion of p-Aminohippuric acid (P.A.H.)

The tubular capacity to excrete P.A.H. at high plasma levels is decreased in the oliguric and early diuretic phases of oliguric failure following injury and other conditions (Brun 1954, Ladd 1955). Taken at its face value, this indicates impairment to tubular function. The effect, like that of glycosuria after tubular loading, can be explained on the basis of two populations of nephrons—one damaged and unable to excrete P.A.H. and the other capable of normal function.

Glomerular Filtration

The inability to explain traumatic uræmia by tubular damage necessitates reassessment of glomerular function. There is no doubt that the clearances of inulin and endogenous creatinine are greatly reduced during traumatic and hæmorrhagic shock, in oliguric uræmia, and in the early diuretic phase (Eggleton et al. 1942, Corcoran and Page 1943, Lauson et al. 1944, Bull et al. 1950, Brun 1954, Ladd 1955). Low clearances are also found after extensive burns during the period of shock and in the later oliguric or nonoliguric renal failure when this occurs (Dziemian 1948, Graber and Sevitt 1959).

Normally these clearances measure glomerular filtration-rate but this interpretation has been criticised in patients with acute renal failure.

Tubular damage present is said to permit unselective reabsorption or back diffusion of filtered water and solutes; this, not the low G.F.R., accounts for low clearances of inulin, creatinine, and other substances (Phillips and Hamilton 1948) and for the oliguria and azotæmia (Lucké 1946). This concept has bedevilled all conclusions related to glomeruler filtration because it implies that the glomeruli are producing a filtrate but that the rate of filtration cannot be measured by clearance tests. Richards' (1929) observations on the nephrons of frogs poisoned by mercury are cited since he found that glomerular filtration continued but that the filtrate was completely absorbed by the tubules, and so no urine was passed. In these experiments, however, the glomerular blood-flow continued, in contrast to the renal ischæmia in traumatic uræmia. Unselective reabsorption might occur, but its effect would be limited to damaged nephrons, and the result would be a reduction in the number of functioning units which would continue to form urine.

Unselective reabsorption can hardly determine the composition of the urine because little if any of the filtrate would reach the ureter. It cannot be responsible for the low clearance values because the creatinine and inulin clearances in acute renal failure are equally reduced (Corcoran and Page 1943, Brun 1954, Graber and Sevitt 1959) which would be expected if they both measured the G.F.R. This is in contrast to the low and varying ratios of the urea to creatinine clearances (Graber and Sevitt 1959) which indicates tubular discrimination between urea and creatinine. Moreover the very low sodium and chloride and high potassium concentrations in the urine must result from intense tubular activity, and not from unselective reabsorption from tubular damage.

Thus endogenous creatinine and inulin clearances are measures of the *effective* G.F.R.—that is, that part of the glomerular filtrate which produces the urine itself.

Temporary and Persistent Falls in Filtration

Serial estimates of endogenous creatinine clearance showed a considerable fall in the G.F.R. within a few hours of burning and beginning therapy (Graber and Sevitt 1959). The fall was often interrupted by considerable fluctuations, and azotæmia developed when the mean G.F.R. was below 50% of normal for 24 hours. In some cases the G.F.R. returned to normal within a few days, but in others the low G.F.R. (5–20% of normal) persisted or worsened and was unaffected by transfusion; in them azotæmia was severe and generally progressive (fig. 2). Some patients had severe oliguria, others a relatively normal urine flow. In the wounded soldiers studied by Ladd (1955) temporary reduction in filtration was related to moderate injuries and persistent lowering to severe multiple injuries, often with abdominal trauma. Transfusion of large quantities of blood failed to prevent or reverse the severe persistent fall in filtration.

Renal Ischæmia

Renal ischæmia develops in recently injured patients (Lauson et al. 1944), in wounded soldiers (Burnett et al. 1947, Ladd 1955), and in animals subjected to hæmorrhage or trauma (Van Slyke et al. 1944, Keele and Slome 1945). It is due to a selective vasoconstriction because Lauson et al. (1944) found that the fall in renal blood-flow was greater than that of the cardiac output or arterial pressure when these were reduced. Criticism has been made because renal blood-flow was usually measured by the clearance of P.A.H., but it cannot apply to Keele and Slome's experiments in which renal blood-flow was measured directly and by a plethysmographic method. The renal blood-flow apparently is slow to return after injury and this may be related to the ischæmia of renal failure.

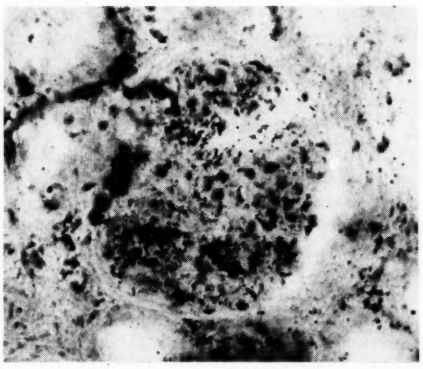

Fig. 6—Glomerulus from a case of acute renal failure after burning. The epithelial cells contain numerous fine droplets of lipid (black dots). Frozen section of kidney stained by oil-red 0 for lipid, ×500.

Renal ischæmia is present in oliguric renal failure, but recent observations indicate that it is not as severe as has been supposed, and is proportionately less than the fall in G.F.R.

Using P.A.H. and the Fick principle, Sirota (1949) and Bull et al. (1950) found a very low blood-flow, down to 10% of normal or even less. On the other hand, Munck (1958), who used a method involving the excretion of radioactive krypton, found that the renal blood-flow in patients with oliguric failure was on the average about a third of normal and considerably greater than that found by P.A.H. clearance. The glomerular filtration-rate was reduced to a much lower level, and thus the filtration fraction $\left(\frac{\text{G.F.R.}}{\text{Renal plasma-flow}}\right)$ was much lower than the normal range. The disproportionate fall in filtration supports the present contention that ischæmia cannot account for the full reduction in glomerular filtration, and that other changes such as those within glomeruli must have contributed.

Maluf's (1949) experiments are also relevant here. Azotæmia, oliguria, and a very low rate of glomerular filtration were produced in dehydrated dogs by intravenous injection of lysed red blood-cells; renal vasospasm was not apparent because in-vivo injection of indian ink showed active glomerular blood-flow. His results can be explained by a grossly reduced filtration in the face of less reduced glomerular blood flow.

The disproportionate fall in G.F.R. relative to blood-flow suggests that changes have taken place within the glomerular capsules.

Changes in the Glomeruli

The glomerular tufts are said to be essentially normal, although in paraffin sections Bowman's capsule often contains eosinophilic exudate and amorphous globules, whilst the parietal epithelium is desquamated and may later show cubical epithelial hyperplasia.

Lipid Droplets

Examination of frozen sections of kidney from patients with acute renal failure after burning often reveals multiple fine droplets of lipid in the epithelium of the glomerular tufts (fig. 6) (Graber and Sevitt 1959). Multiple droplets are usual when tubular necrosis is present or when azotæmia has occurred, but their presence and density are not consistently related to tubular necrosis. The significance of large numbers of fatty droplets has not been fully assessed, but it is not a normal phenomenon and it may reflect a more serious lesion.

Electronmicroscopy of the normal glomerulus (Pease 1955) shows that the capillary endothelium is full of fine pores about 0·1 μ in diameter, and that the epithelial cells have multiple gaps or fenestrations between fine foot-like processes cemented to the basement membrane. The pores and gaps must mean that the only structure normally capable of filtration is the intervening basement membrane. It is conceivable that subtle glomerular changes impossible to define by light microscopy may develop in patients with acute renal failure and contribute to the persistence in the fall of glomerular filtration. Changes such as acute cellular swelling with obliteration of pores or reduction in fenestrations might oppose filtration. Thus the appearance of many fatty droplets might possibly be a histological sign of a more serious lesion hindering filtration not visible by light microscopy. Electronmicroscopy of the glomeruli from cases of traumatic uræmia is awaited with interest.

Pathogenesis

A schematic outline of the present concept is shown in fig. 7. A full explanation is not yet possible, but renal

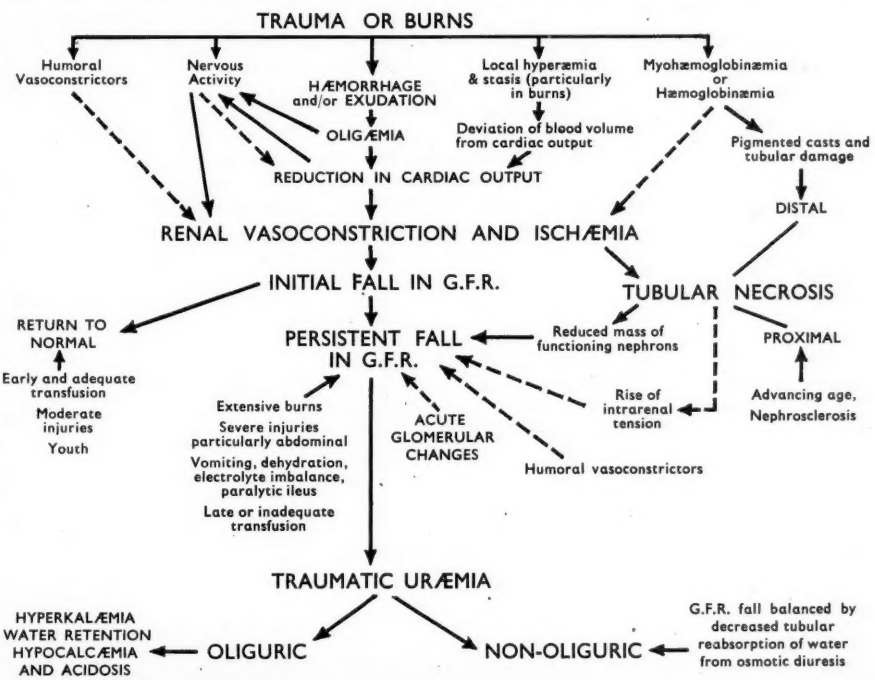

Fig. 7—Diagram outlining the pathogenetic mechanisms involved in traumatic uræmia and tubular necrosis. The broken arrows indicate possible or probable factors.

ischæmia and low glomerular filtration have emerged as the central features.

Renal Ischæmia and Low Glomerular Filtration

Renal ischæmia is initiated by vasoconstriction induced by oligæmia and a fall in cardiac output, but the manner in which it is maintained is uncertain.

Among the possible causes are a rise of intrarenal tension, and humoral vasoconstrictive agents such as noradrenaline, renin, and 5-hydroxytryptamine. The tense capsule and swollen appearance of the kidney, together with the interstitial œdema and inflammatory exudate, suggest that intrarenal tension is increased. On the other hand a normal tension was found in dogs with tubular necrosis produced by ligation of the renal artery (de Wardener 1955) and in patients with acute renal failure (Munck 1958). The persistent ischæmia warrants further investigation.

Renal ischæmia presumably initiates the fall in glomerular filtration, and to some extent maintains it, but changes within the glomeruli may play a part in the latter. This aspect of the problem also requires further study, and the finding of multiple lipid droplets in the glomerular epithelium of burned patients suggests that subtle changes opposing filtration may have occurred.

Role of Hæm Compounds

Hæm pigments are now considered to act as subsidiary and potentiating factors. Release of pigment may turn the scales of a subclinical renal effect or worsen the result of dehydration and shock.

Thus, intravenous injection of lysed red blood-cells produced little change in glomerular filtration unless the dog was previously dehydrated (Maluf 1949); hæmoglobin precipitated fatal uræmia only in animals previously subjected to a short period of renal ischæmia, or given a nephrotoxic drug such as sodium tartrate (Yuile et al. 1945, Badenoch and Darmady 1948); whilst myohæmoglobin produced uræmia in rats only when dehydration was produced and the legs were crushed (Corcoran and Page 1945).

Hæmoglobinuria is very common in patients with acute renal failure after burning, particularly those who develop diffuse distal tubular necrosis, yet it is relatively uncommon in those who die without renal failure (Sevitt 1956a and b). Azotæmia and distal tubular necrosis seem to be reduced or prevented in some burned children with severe hæmoglobinuria if the blood-volume is prevented from falling. Pigmented casts then become few as if they were washed out by the flow of tubular urine (see Sevitt 1957). Both renal ischæmia and deposition of many casts are apparently necessary in most instances of diffuse distal tubular necrosis after burning.

Discussion and Summary

The concept that tubular damage is the basis of traumatic uræmia, and that oliguria and uræmia are related to back diffusion of the filtrate through damaged tubules, is no longer acceptable. Firstly, uræmia without oliguria cannot be explained by nonspecific tubular reabsorption or blockage by casts, and neither severe oliguria nor the onset of postoliguric diuresis are adequately accounted for by tubular damage and repair. Secondly, tubular necrosis is more common than renal failure in patients at risk, and moreover traumatic uræmia may occur without tubular necrosis. Thirdly, the electrolyte and other composition of the urine and the absence of glycosuria indicate continued proximal and distal tubular activity even though the patient is found to have extensive tubular damage. The pattern of electrolyte excretion can be explained by the hormonal reaction of the body but not by impairment of tubular function. Fourthly, hyperkalæmia, hypocalcæmia, hyperphosphatæmia, and acidosis result from severe oliguria and not tubular necrosis; they are not characteristic of non-oliguric renal failure even though tubular necrosis is found.

The alternative concept is that renal failure is precipitated and maintained by a low rate of glomerular filtration, whilst the common association of uræmia and tubular necrosis results from common pathogenetic factors particularly renal ischæmia (fig. 7). The development of uræmia without tubular necrosis and vice versa reflects other influences. These include release of hæm compounds, which enhance the likelihood of distal tubular necrosis; possibly vasoconstrictive humoral agents and differences in tubuloepithelial sensitivity to ischæmic hypoxia; and subtle changes within the glomeruli opposing filtration, of which fatty glomerular droplets may be a visible sign.

Tubular necrosis never involves all the nephrons. The proportion affected varies, and affected kidneys have two populations—damaged and functioning nephrons. The damaged ones form little or no urine, possibly because of back diffusion of the filtrate or blockage by casts, but they reduce the number of functioning units and further diminish the rate of glomerular filtration. The filtration-rate is, however, lower than this can account for, and indeed tubular necrosis is sometimes absent. Tubular damage may well be responsible for the diminished powers revealed by maximum loading with *p*-aminohippuric acid and glucose, but these are summation effects combining the ineffectiveness of damaged nephrons and the activity of the normal ones.

Functioning nephrons are responsible for the urine, for its electrolyte composition, and for the reabsorption of glucose; their tubules can deal with the filtration loads of glucose, sodium, and chloride, and excrete considerable concentrates of potassium, thereby responding to the demands of increased aldosterone secretion. The filtration load of solutes, is however, reduced by the lower filtration.

Oliguria is adequately explained by the low G.F.R., and other explanations, such as back diffusion or blockage of the filtrate by casts, are unnecessary. The rate of urine-flow is determined by the balance between the reduced G.F.R. and the reduced tubular reabsorption of water; reabsorption of water is decreased even when oliguria is severe. Oliguria occurs when the decreased reabsorption is insufficient to balance the fall in G.F.R., but, when a balance has been achieved, the flow of urine is adequate. The reduced tubular reabsorption of water may be interpreted teleologically as a compensatory attempt to maintain the water balance of the body in the face of a low G.F.R., and is reminiscent of a similar phenomenon in chronic renal failure (Platt 1951). When compensation fails oliguria occurs, with all its limitations in the excretion of potassium, phosphate, and hydrogen ions. In this way the persistent fall in G.F.R. can be responsible for water retention, hyperkalæmia, hyperphosphatæmia (and thereby hypocalcæmia), and acidosis as well as azotæmia.

Thanks are due to colleagues for their interest, and to Mr. R. Gill and Mrs. V. Smith of the photographic department for their help.

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GENES ON THE Y CHROMOSOME INFLUENCING RATE OF MATURATION IN MAN

SKELETAL AGE STUDIES IN CHILDREN WITH KLINEFELTER'S (XXY) AND TURNER'S (XO) SYNDROMES

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IT has long been known that girls are physically more mature than boys at all ages from birth to adulthood. In skeletal maturity, judged by the appearance and progressive development of ossification centres, girls at birth are advanced by a matter of weeks, at primary-school age by months, and at adolescence by the two years which separate the sexes in their growth spurts and in the age at which they reach adult height. This sex difference begins early in intrauterine life; the centre for the talus, for example, appears an average of 2 weeks earlier in girls (22–29 weeks) than in boys (24–32 weeks). The chimpanzee, the rhesus monkey, and, apparently, the rat, have a similar sex dimorphism. Other indicators of developmental age, such as the dentition and the velocity of growth in physical measurements, show the same distinction. Each permanent tooth erupts earlier in girls and in female apes and monkeys. The pattern of velocity and acceleration in the average girl's growth curve of stature is at a given chronological age similar to that shown by the average boy's curve somewhat later (see Tanner 1955, p. 51).

The cause of this striking difference is quite unknown. The recent demonstration by Ford, Jacobs, and others (Jacobs and Strong 1959, Ford, Jones et al. 1959) that most patients with Klinefelter's syndrome have the chromosomal formula XXY and those with gonadal dysgenesis XO now makes it possible to find out whether genes on the Y chromosome are responsible. We are in a position to see whether XXY individuals follow the development-rate of boys (XY) or of girls (XX), and whether the lack of the second X chromosome accentuates or retards the rate of development of XO individuals.

Material and Methods

We have investigated the skeletal age of 27 individuals between the ages of 6 and 18 with Klinefelter's syndrome. 19 of these came from Zurich and 8 from Glasgow. The characteristics of a number of them have been reported previously (Prader et al. 1958, Ferguson-Smith 1958, 1959). It should be remembered that all were mental defectives.

The skeletal ages, taken from the hand and wrist, were assessed by reference to the Greulich-Pyle Atlas (Greulich and Pyle 1950), and since we had no guarantee that normal Zurich and Glasgow children agreed with these American norms we assessed also, as controls, 47 normal boys and girls of matched age distribution in Zurich and 21 boys drawn at random from a large sample of normal children in Kilmarnock, close by Glasgow, whose X-rays were taken in a study providing the basis of new, but as yet incomplete, standards of skeletal age (J. M. Tanner, M. J. R. Healy, and R. H. Whitehouse; unpublished).

Measurements of height and weight were available for most of these patients and for 9 of their normal brothers. The percentile status and height and weight age were assessed for the Zurich children by reference to Heimendinger's (1958) standards for Basle children, and for Glasgow children by Cheeseman and Walby's (1954) standards for Belfast children, which latter probably approach the Glasgow norm better than Provis and Ellis's (1955) standards for Edinburgh children, and certainly much better than Tanner's (1958) standards for English children.

We have investigated also 9 children from Zurich with untreated Turner's syndrome, aged 7–18, 8 with known male nuclear sex, 1 untested. In addition, hand X-rays were available for 8 cases of Turner's syndrome aged 1–14, in the files of The Hospital for Sick Children, Great Ormond Street, London. We are indebted to Dr. L. G. Blair, Dr. R. E. Bonham-Carter, Dr. P. R. Evans, Dr. A. P. Norman, Dr. B. E. Schlesinger, and Sir Wilfrid Sheldon for permission to study these last patients and their X-rays.

RATIO OF SKELETAL AGE (GREULICH-PYLE) TO CHRONOLOGICAL AGE IN CONTROLS AND PATIENTS: KLINEFELTER'S SYNDROME CASES RATED ACCORDING TO BOYS' STANDARDS, TURNER'S SYNDROME CASES RATED ACCORDING TO GIRLS' STANDARDS

—	Controls		Klinefelter's syndrome		Turner's syndrome			
	Zurich	Kilmarnock	Zurich	Glasgow	Zurich	London	Baltimore*	Philadelphia†
No.	47	21	19	8	8	8	19	5
Age (yr.) ..	6–17	7–12	6–23	7–12	7–15	1–14	1–17	1–17
Range ..	0·70–1·07	0·63–1·04	0·66–1·10	0·65–0·90	0·69–0·95	0·72–1·00	0·73–1·67	
Mean ..	0·93	0·88	0·90	0·82	0·79	0·82	0·95	0·87
S.E. mean ..	0·01	0·03	0·02	0·03	0·04	0·04	0·04	

* Grumbach et al. 1955. † Mellman et al. 1958.

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Results

The results are summarised in the accompanying table.

Skeletal Age

The skeletal ages of the Klinefelter's syndrome patients were estimated by reference to the *male* standards, for reasons shortly to become apparent. The majority of these patients are slightly retarded over the Greulich-Pyle norms: the skeletal-age/chronological-age ratio covers a range of 0·66 to 1·10 in the Zurich cases, and 0·65 to 0·90 in the Glasgow ones. The means are $0{\cdot}90\pm0{\cdot}02$ for Zurich and $0{\cdot}82\pm0{\cdot}03$ for Glasgow. The Greulich-Pyle standards, however, are taken from an economically superior group of American children, and some retardation in relation to them is probably to be expected. In fact, the 47 control Zurich children have a mean ratio of $0{\cdot}93\pm0{\cdot}01$ with a range of 0·70 to 1·07. This degree of retardation is the same for both sexes and at all ages. Allowing additionally for the fact that mentally subnormal children are in general slightly retarded compared to bright children we see that the Zurich Klinefelter's syndrome cases fit the pattern of the normal *male* very closely. The same is true of the Glasgow cases: the 21 Kilmarnock control boys have a mean ratio of $0{\cdot}88\pm0{\cdot}03$ with a range of 0·63 to 1·04. The Glasgow Klinefelter's syndrome mean is slightly, but insignificantly, less.

If the Klinefelter's syndrome patients had been compared to the normal female standards, however, the retardation would have been very large. Since a boy is normally about 0·80 times the skeletal age of a girl of the same chronological age the Klinefelter's syndrome patients would have averaged only 0·72 in Zurich and 0·66 in Glasgow, whereas the control figures would, of course, be unchanged. Thus it is clear that *XXY leads to the same skeletal age as XY, at least throughout the age range 6–18.*

Patients with Turner's syndrome, on the other hand, are usually said in published reports to have a normal or only slightly retarded bone age, and this by reference to *female* standards. The 8 cases we have studied in London uphold this belief; related to the female standards their average ratio is $0{\cdot}82\pm0{\cdot}04$, with a range of 0·72 to 1·00. This is perhaps slightly retarded compared with what we would expect normal girls of similar locality and social background to be, but only slightly. Related to male standards the London Turner's syndrome average would be 1·00, which is distinctly in advance of our normal children. The Zurich patients under the age of 18, however, had an average skeletal-age/chronological-age ratio of $0{\cdot}79\pm0{\cdot}04$ with a range of 0·68 to 0·95. This is distinctly below the expected normal average of 0·93 at Zurich. Relative to *male* standards, however, these children would be about as much advanced as they are retarded relative to female ones. There is also an additional fact pointing to their equivalence with females rather than with males. The Turner's syndrome cases, unlike the Klinefelter's, show a greater degree of asymmetry of development amongst the various epiphyses than is normal. In this they seem to resemble hypopituitary dwarfs. It looks as though there is some added defect over and above any simple action on general rate of development. The presence of such a defect, would, of course, harmonise with the reduction of height growth in Turner's syndrome and with the frequent presence of other skeletal anomalies. The 19 cases between 1 and 17 years of age reported by Grumbach et al. (1955) give an average ratio of $0{\cdot}95\pm0{\cdot}04$, and the 5 cases of the same age range reported by Mellman et al. (1959) an average of 0·87. Both these groups of investigators used an appearance-fusion system for bone age, which may be less sensitive to pathological defects of shape and developmental asymmetry than the Greulich-Pyle method.

We may conclude, therefore, that, though in Turner's syndrome there is probably some slight retardation compared with the girls' standards, together with abnormal asymmetry of development, in general *XO leads to approximately the same skeletal age as XX.*

Height, Weight, and Body Build

The Zurich Klinefelter's syndrome patients are mostly tall for their age despite their mental deficiency, which is usually associated with reduced stature. The range of their percentile status is from 20 to 95, with an average figure of 67 based on 20 cases. There is no difference between those who have reached adult or near-adult height and those who have not; the average percentile for the 12 cases less than 15 years of age is 64. 9 brothers of 7 patients were measured; and 7 had a lower percentile for height, 1 the same percentile, and only 1 a higher percentile. The excess height of Klinefelter's syndrome patients is in each instance due to abnormally long legs. The pubis-head measurement is normal for boys of the same chronological age, but the pubis-heel measurement is excessive. This is equally true before puberty as during and after it. The span, though difficult to evaluate because of lack of adequate standards and techniques, may be somewhat increased also, though less than the leg length. Raboch and Maly's (1957) 5 adult patients had a normal forearm length, together with long legs, slightly reduced trunk length, and much reduced shoulder width.

The Glasgow patients were less tall, with an average percentile of 38 and a range of 10 to 60.

In each instance weights keep pace, more or less, with heights. The Zurich children have an average percentile status of 60, with those under 15 years averaging 62. The Glasgow children average 27. The explanation for the discrepancy between the two series is probably that the Glasgow children's intelligence quotients (I.Q.s) ranged from 45 to 85, whereas the Zurich children's were all between 75 and 85. Children with a really low I.Q. are frequently very small.

Besides their long legs, the Klinefelter's syndrome children have other features of a feminine—or, perhaps more accurately, eunuchoid—bodily appearance. We have not made the detailed studies which alone could establish the degree to which the feminine or eunuchoid physique is approached, but frontal view photographs of 18 patients certainly suggest a striking lack of mesomorphy, together with a somewhat greater similarity of appearance than one would expect in 18 boys chosen at random.

The Turner's syndrome cases, as is well known, are small in stature at all ages, even compared with girls' standards. Most of the Zurich cases are below the first percentile for height, and, with two notable exceptions (90th and 75th percentiles), for weight.

Discussion

Maturity

XXY individuals have a rate of skeletal maturation corresponding to XY, and XO individuals a rate corresponding to XX. Thus, Y produces retardation in the presence of either one or two Xs, and without Y neither one nor two Xs produce this effect. It follows that genes on the Y chromosome are the cause of the normal sex difference in rate of development. Though until recently the Y chromosome in man was thought to be inert, it is now clear that genes upon it are the cause of the differentia-

tion of the primary gonad into a testis rather than an ovary. The further differentiation of the external genitalia into penis and scrotum is believed to be due to the action of androgens produced by the fœtal testis rather than to direct action of the Y chromosome genes in the tissues concerned.

The male delay in maturation might be brought about by either of these mechanisms—that is, directly or by the fœtal-testicular hormones. A direct action seems more likely, however, since androgens in all other instances cause an advance, not a delay, in maturation. The differentiation of the testis occurs at about the 7th intrauterine week. We do not know at exactly what stage of fœtal life the male retardation of development begins, but there is reason to think it may be just about this time. At 20 weeks the male is about 2 weeks retarded (Pryor 1923), at 40 weeks about 4 weeks retarded; at 10 weeks he might well be 1 week retarded, and this would denote action of the Y chromosome at 7 weeks or earlier. It is tempting to think that the factors causing retardation and those causing gonadal differentiation may be closely related.

The mechanism whereby the male maintains his relative retardation throughout the growing period is totally obscure. The only hormone that might be implicated, on present information, is the thyroid. In young rats administration of thyroid hormone accelerates skeletal development, tooth eruption, and eyelid opening (Walker 1957), though the effect diminishes under experimental conditions as the time of administration is prolonged. In man clinical hypothyroidism causes a delay in all phases of development and hyperthyroidism an advance. The same is true in monkeys (see Tanner 1955, p. 124). The very meagre data on thyroid function in normal boys and girls, however, gives no indication of any sex difference. The figures of Martman et al. (1956), for example, on the ^{131}I uptake of prematures a day after birth give identical averages for boys and girls of 1500–2500 g, as do those of Oliner et al. (1957) from birth to 18.

There seems to be some mechanism in the tissues themselves, on the other hand, for controlling their speed of development. It is very striking how after a period of disease or malnutrition causing retardation of growth and development a " catch-up " phase follows during which the velocity may exceed greatly the normal rate of growth and maturation. But this " catch-up " rate slows down to normal as the child reaches its previously established growth curve. This suggests that the control of maturation is based on signals from the tissues themselves, even if these signals act by affecting the release of a hormone centrally.

Body-build

The effect of genes on the Y chromosome in controlling body build is at present not clear. It is worth noting, however, that long before puberty a sex dimorphism is present, boys being more muscular, or more generally mesomorphic in shape, than girls (see Tanner 1955, p. 43). This, however, is clearly *not* simply due to the presence of the Y chromosome, since XXY children in general do *not* resemble XY children in build.

The 16 chromatin-positive Klinefelter's syndrome adult patients studied by Stewart et al. (1959) showed a significantly greater length of leg than either controls from the same infertility clinic or chromatin-negative Klinefelter's syndrome adults. As in our children, lengths of trunk were similar in all groups. Our data extend this finding down to prepubescent ages, and show clearly that the abnormally great leg length is not due to delayed epiphyseal closure, but to a greater growth-rate from an early age. Just how early it begins is a question full of interest. There are a number of finely regulated growth gradients during development, so that, for instance, the head end of the organism is at any time nearer final completion than the base of the spine, the hands than the forearm and upper arm, and the feet than the calf and thigh. The legs bring up the rear in this procession; they are laid down last and are least developed at birth. A very small variation from normality at the time of establishment of the initial gradient would result, one might suppose, in a continuously increased or diminished growth velocity subsequently. An example is provided by the normal sex difference in length of forearm relative to upper arm, which results from the boys' relative velocity of forearm being just slightly more than the girls' throughout the whole growth period (see Tanner 1955, p. 37).

Since in respect of leg length XXY children resemble XX even less than XY we cannot ascribe the long legs to the action of X chromosomes either. It seems more likely to be due either to an early imbalance in differentiation or else to a lack of secretion of some " male " hormone. This must occur, however, at some stage *after* the time at which the external genitalia and genital ducts are laid down, since their normality in XXY persons argues a near-normal secretion during early fœtal life.

The lack of mesomorphy in the XXY individuals, if it can be established more firmly in future cases, would be an important result, since it would show that differentiation of muscle is also not primarily dependent on the Y chromosome, either directly or through the secretion of fœtal-testicular androgens. In this characteristic the XXY *does* resemble the XX. Too few studies of physique in Turner's syndrome have been made for us to know what the complementary situation, of XO, leads to so far as mesomorphy is concerned. We do have the general impression that XO children are frequently as mesomorphic as the XXY.

As a working hypothesis then, we suggest that it is the double dose of X which chiefly inhibits the development of muscular differentiation and the mesomorphic body build. That a few Klinefelter's syndrome patients are fairly well muscled as adults does not necessarily disprove this hypothesis, since they have been subjected to the action of male androgens at puberty, as women are not. Our theory would only demand that they should not exceed in mesomorphy the level reachable by women appropriately treated with androgens. Disproof would, however, follow the finding of a Klinefelter's syndrome patient who was *highly* mesomorphic, but we have not seen one to date. Klinefelter's syndrome children, considered as males, seem in many ways to be at the opposite pole to the extreme mesomorph, who is advanced relative to other boys in bone age (Dupertius and Michael 1953), short for his age, relatively short-legged, and " masculine " in appearance.

Summary

Girls are ahead of boys in skeletal development and other signs of physical maturity from before birth to adulthood. Light has been thrown on the mechanism of this sex dimorphism by the assessment of skeletal age in 27 individuals between the ages of 6 and 18 with Klinefelter's syndrome, and in 16 individuals with Turner's syndrome. The former children, with chromosomal

formula XXY, have a skeletal age equivalent to normal males XY; the latter, of formula XO, a skeletal age approximately equivalent to normal females XX.

It is concluded that genes on the Y chromosome are responsible for the sex dimorphism in rate of development in man and other primates. The action of the Y chromosome in causing differentiation of the primitive gonad into a testis is evident at about 7 intrauterine weeks, and the retardation of development in the male probably begins at about this time also. There is a possibility that the two actions are closely related.

The Klinefelter's syndrome children have longer legs than is normal at all ages studied, though their trunk length is quite usual. Since this characteristic appears before puberty it is due, not to delay in epiphyseal fusion, but to a fundamental difference in growth-rate. Besides this our impression is that the great majority are somewhat feminine or eunuchoid in appearance and distinctly lacking in mesomorphy or degree of muscularity. If this impression is substantiated it would follow that the sex dimorphism in mesomorphy, which is certainly present before puberty is due primarily, *not* to the action of the Y chromosome, but to a double dose of X-inhibiting muscular differentiation and development.

We wish heartily to thank Prof. Alan Moncrieff for his critical encouragement of these studies, and Mr. R. H. Whitehouse for his skilled assistance.

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TREATMENT OF TROPICAL EOSINOPHILIA
A CONTROLLED TRIAL

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UNTIL recently the standard treatment for tropical eosinophilia consisted in the administration of an arsenical preparation over a period of weeks (Weingarten 1943). We describe here a comparison of results with this treatment and with treatment by the new drug, diethylcarbamazine (Ganatra and Lewis 1955, *Lancet* 1958).

Material and Methods

Clinical Material

The cases studied were selected from patients attending the medical and pædiatric outpatient clinics of the Christian Medical College Hospital, Vellore. All cases were referred to a special clinic which was held twice weekly, and each patient was seen personally and followed throughout by one of us.

The criteria used in selecting cases were: (1) the presence of respiratory symptoms and signs; (2) an absolute eosinophil count of over 4000 per c.mm.; (3) the absence of other causes of eosinophilia, such as intestinal parasitic infection; (4) the absence of other causes for the respiratory symptoms; and (5) the ability of patients to attend for follow-up. Patients who were unable to attend regularly for follow-up were excluded from the investigation.

Hæmatology

Absolute eosinophil counts were done by the method described by Dacie (1956). All apparatus was standardised, and all counts were done by the same technician.

Therapeutic Trial

Patients on first attending the clinic had a complete physical examination, and the following investigations were carried out: (1) absolute eosinophil count; (2) examination of three stool specimens for parasites; (3) examination of three sputum specimens for acid-fast bacilli and parasites; (4) examination of three random specimens of blood for microfilariæ; and (5) chest X-ray. All patients fulfilling the stated criteria were then included in the trial.

Patients with parasites in their stools were treated with appropriate therapy; if eosinophil counts, repeated after two weeks, were still above 4000 per c.mm., these patients were included in the trial if otherwise eligible.

The numbers 1–75 were allotted at random to three equal groups designated A, B, and C, only the pharmacist being aware which numbers were in each group. Patients accepted into the trial were allotted a serial number 1–75, as they presented, and thus they were placed at random into one of the three groups.

All patients were given a course of tablets for one week, and a series of injections twice weekly for five weeks. Those in group A received placebo tablets and placebo injections which were indistinguishable from true diethylcarbamazine tablets and true 'Acetylarsan' (diethylamine-acetarsol) injections. Those in group B received placebo tablets and true acetylarsan injections. Those in group C received true diethylcarbamazine tablets, and placebo injections. "Diethylcarbamazine" tablets, true or placebo, were given at a dosage level of 10 mg. per kg. of body-weight per day for seven days, and "acetylarsan" intramuscular injections, true or placebo, according to the following dosage schedule:

For children under 20 kg. body-weight, 0·5 ml. for the first injection, 0·75 ml. for the second, and then 1 ml. twice a week. Children over 20 kg. body-weight were given 0·5 ml., 0·75 ml., and 1 ml., and then 2 ml. twice a week. The preparation used for children receiving true arsenic contained 0·02 g. of arsenic per ml. Adults received 0·5 ml. for the first injection, 1 ml. for the second, and 2 ml. thereafter. The preparation used for adults receiving true arsenic contained 0·05 g. of arsenic per ml.

The clinician was never aware of the group to which the patient belonged; appropriate doses of "diethylcarbamazine" and "acetylarsan" were ordered, and the patient's number quoted. The pharmacist then dispensed the respective true or placebo medicines according to whether the patient was in group A, B, or C. All patients were seen twice weekly. At each visit the patient's condition was carefully assessed by history, physical examination, and absolute eosinophil counts, and a careful watch was kept for any evidence of toxicity.

A patient was considered to be cured only when symptoms and signs disappeared, and the eosinophil count returned to less than 2000 per c.mm.

In each case after completion of the five weeks' course of treatment, observation of the patients who were cured was continued for at least two months. Patients who were not cured at the end of five weeks were removed from the trial and treated, usually with diethylcarbamazine.

Dosage Schedule of Diethylcarbamazine

At the conclusion of the controlled trial, in order to determine the best dosage and duration of treatment with diethylcarbamazine, cases were allotted at random into six groups each of 15 cases, receiving 5 mg. per kg. body-weight per day for seven days and three days, 3 mg. per kg. body-weight for seven days and three days, and 1 mg. per kg. body-weight for seven days and three days respectively; and the responses in these groups were compared.

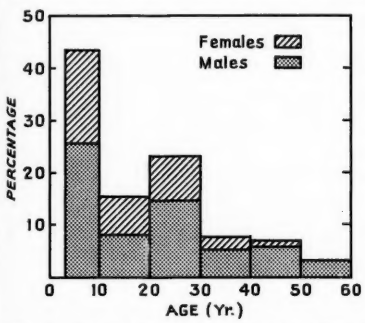

Fig. 1—Age and sex distribution of patients studied.

Clinical Features

A total of 165 patients were studied. They were all Indians, the majority belonging to the poorer classes and coming from the town of Vellore and surrounding rural areas. The age and sex distribution of cases is set out in fig. 1. The preponderance of males over females in the ratio of 3 : 2 is the same as the overall sex-distribution of patients attending the hospital. The maximum prevalence was in the age-group 3–10 years (43%).

DURATION OF SYMPTOMS AT FIRST VISIT TO HOSPITAL

Duration (months)	No. of cases
Under 1	48
Over 1 to 3	49
Over 3 to 6	31
Over 6 to 12	23
Over 12	14
Total	165

The duration of illness at the time patients were first seen varied from a few weeks to two years, but 59% of the cases had had their symptoms for three months or less (see accompanying table).

Symptoms elicited when the patients were first seen are shown in fig. 2. All patients had respiratory symptoms of some sort. 94% complained of cough; in half of these the cough was worse at night than in the day. 88% of the patients complained of attacks of dyspnœa and some of these had been treated elsewhere as cases of bronchial asthma. 56% of the patients stated that they had lost weight and 44% complained of moderate fever. A third of the patients who had fever complained of right hypochondrial pain. 2 patients had had hæmoptysis for which no other cause could be found, and 2 male patients complained of mild testicular pain.

In only 2% of patients was there any history suggesting a previous allergic disorder. In 10% of patients there was a family history of a similar complaint in the past, but in no case were we able to examine more than one active case in a family.

Clinical examination revealed pulmonary signs in all cases. Rhonchi—expiratory, or expiratory and inspiratory—were present in 53% of cases, and were usually combined with prolonged expiration. Medium or coarse crepitations were present in 45% of cases, and fine crepitations in 13% of cases. 16·5% of patients had enlarged lymph-glands, often most notably in the cervical region. In no case were the glands more than 2 cm. in diameter, and in all cases the glands subsided with successful treatment. In 24% of patients the liver was enlarged 1–8 cm. below the right costal margin; and in a third of these there was associated splenomegaly, the spleen varying in size from "just palpable" to 4 cm. below the left costal margin.

X-ray Findings

Chest X-rays were taken in 149 cases. In 25 of these no abnormality was detected; in 101 there were increased markings or linear striations throughout the lung fields, and in 23 there was diffuse mottling.

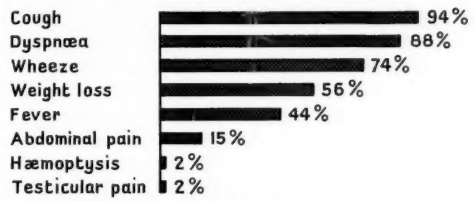

Fig. 2—Symptoms elicited at first visit to hospital.

Eosinophil Counts

Total eosinophil counts ranged from 4000 to 46,000 per c.mm. with an average of 13,720 per c.mm. The frequency distribution of the initial counts is set out in fig. 3.

Results

Of the 25 patients in group A (placebo tablets and placebo injections) none improved spontaneously during the period of observation. At the end of six weeks, patients in this group were taken out of the trial and treated with a known active preparation.

Of the 25 patients in group B (acetylarsan injections and placebo tablets) 15 responded after various periods, but 7 of these subsequently relapsed. 10 patients showed little or no improvement.

Of the 25 patients in group C (placebo injections and diethylcarbamazine tablets) 24 responded, and in general the response was quicker than in the group treated with

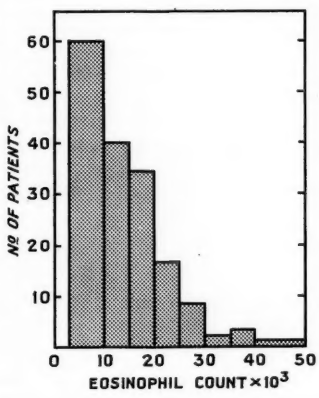

Fig. 3.

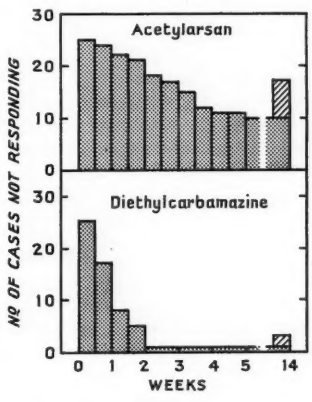

Fig. 4.

Fig. 3—Frequency distribution of initial absolute eosinophil counts.

Fig. 4—Response to treatment with acetylarsan and diethylcarbamazine. The black areas represent the number of cases not responding to treatment at any given time; the dotted areas represent cases which relapsed.

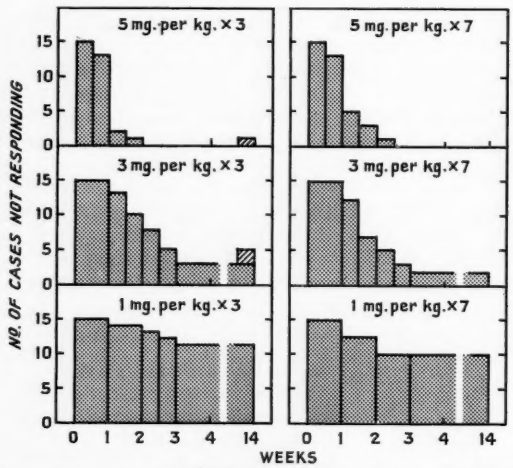

Fig. 5—Response to treatment with various dosages of diethylcarbamazine. ×3 and ×7 indicates treatment given for 3 days and 7 days. Doses are in mg. per kg. of body-weight per day. The black areas represent the number of cases not responding to treatment at any given time; the dotted areas represent cases which relapsed.

arsenic. At the end of the first week, 17 out of 25 cases had responded, compared with 3 out of 25 of the cases treated with arsenic. 1 case responded partially, in that symptoms and signs were relieved but the eosinophil count remained increased. 2 of the patients in this group subsequently relapsed.

The results are set out diagrammatically in fig. 4.

Since the composition of the groups with respect to age, sex, and duration of illness was similar, the test for proportions, using the normal curve, was applied to the results; and the difference in response between groups B and C is highly significant at the 0·01 level.

In this series no toxic symptoms or signs were noted with either arsenic or diethylcarbamazine.

Effect of Varying Dosage of Diethylcarbamazine

Patients receiving 5 mg. of diethylcarbamazine per kg. of body-weight per day for seven days showed a response identical with that of patients receiving 10 mg. per kg. of body-weight per day, all of 15 patients responding by the end of two and a half weeks. Similarly, each of 15 patients treated with 5 mg. per kg. of body-weight per day for only three days showed an adequate response by the end of two weeks; but 1 of these patients subsequently relapsed.

Patients treated with 3 mg. per kg. of body-weight, however, responded rather more slowly; of the 15 patients given this dose for seven days, 2 did not respond, and of 15 cases given the dose for three days 3 did not respond and 2 subsequently relapsed. Of 30 patients treated with 1 mg. per kg. of body-weight per day, 21 did not respond.

These results are set out diagrammatically in fig. 5.

Discussion

Clinical Features

The clinical features of these cases in general resemble those described by others (Ball 1950, Danaraj 1958, Webb 1958). The frequency of hepatosplenomegaly in this series is worthy of note. Hepatomegaly was first reported by Ball (1950), but he did not consider it to be a significant finding. Webb (1958) drew attention to the importance of this finding, which emphasises the fact that the disease is a generalised disorder, and not just a disorder affecting the pulmonary and hæmopoietic systems.

The age-distribution of our cases agrees with that of the series previously reported by Ball (1950) from this institution, but is different from that described by others, including Danaraj (1958) who reports a prevalence of only 3·6% in the age-group 0–9 years among affected Indians in Singapore. This difference may be due to true differences in the age-distribution in different places, but on the other hand the high prevalence among children here may reflect the active cooperation we have had from the pædiatric department, and perhaps represents a truer picture of the real overall age-distribution.

Controlled Trial

This controlled trial leaves no doubt that diethylcarbamazine is superior to acetylarsan given in the usually accepted dosage. With diethylcarbamazine a greater proportion of cases were cured, and cure was brought about more quickly. Further, no serious complications have been reported from diethylcarbamazine therapy, whereas occasionally arsenic produces quite serious complications (Viswanathan 1947).

Dosage of Diethylcarbamazine

The results of the trial with varied dosages of diethylcarbamazine suggests that a dose of 5 mg. per kg. of body-weight per day, given for three days, is as effective as 10 mg. per kg. of body-weight given for a week.

This dosage level is considerably less than that recommended by Danaraj (1958) working in Singapore. Danaraj used doses of 12, 18, and 30 mg. per kg. of body-weight per day and found better results with 18 and 30 mg. than with 12 mg. However, our results with 10 mg. and 5 mg. per kg. per day appear to be comparable to those obtained by Danaraj with 18 and 30 mg. per kg. The reason for this apparently greater sensitivity of our patients is not clear, but the possibility of different ætiological agents must be borne in mind. It does not appear to be attributable to the different age-distribution of our patients, as in our series adults responded equally as well as children. Similar small daily doses have also been used in India with good results by Patwari (1958) and by Viswanathan and Krishnamurthi (1958).

The fact that 5 mg. per kg. of body-weight per day appears to be just as effective when given for three days as when given for a week suggests that the initial dose may be the important factor in producing cure. This view is supported by the reports of good responses following single intramuscular injections of diethylcarbamazine (Viswanathan and Krishnamurthi 1958, Shah and Seth 1958). A trial to determine whether a single oral dose is as effective as treatment spread out over days is at present in progress.

The ready and rapid response of this disease to diethylcarbamazine is further evidence that it may be caused by a parasitic infestation—probably some form of filaria.

Summary

165 cases of tropical eosinophilia have been studied. 43% of the patients were under 10 years of age. 24% had hepatomegaly.

A controlled blind trial of placebo, arsenic, and diethylcarbamazine was carried out in 75 cases.

Diethylcarbamazine proved the more effective drug, the difference between the results with this and with arsenic being statistically highly significant.

Diethylcarbamazine 5 mg. per kg. of body-weight per day for three days appears to be adequate therapy for the disorder as seen in South India.

Our thanks are due to Prof. J. Webb for his constant help and encouragement, and for referring cases to us; to the medical staff of the hospital for referring cases under their care; to Mr. Galen Christian for carrying out the blood counts; to Miss J. Sanders, pharmacist, for dispensing the medicines; to Dr. D. E. Paterson for reporting on the X-ray films; to Mr. P. S. S. Sunder Rao for the statistical analysis; to Mr. J. Gajaraj, hospital record librarian, for his assistance; and to Burroughs Wellcome Private Ltd., India, for a generous supply of diethylcarbamazine ('Banocide') tablets and for making identical placebo tablets for the trial.

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PARASPINAL ACRYLIC INLAYS
IN THE TREATMENT OF CERVICAL AND LUMBAR SPONDYLOSIS AND OTHER CONDITIONS

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IN degenerative and traumatic lesions of the spine referred pain arising from deep ligaments and joint capsules, which are affected by inflammatory processes or altered mechanical stress (Kellgren 1939), is probably a more important cause of disability than pain produced by nerve compression.

Immobilisation of acutely painful or unstable joints is a logical method of relieving referred pain. But existing methods of spinal grafting by bone involve lengthy operations and a fairly long stay in hospital. Hence stabilisation is practised infrequently and only in the most severe cases. More often external support is provided, which means that the patient has to wear clumsy apparatus for a long time, or even indefinitely.

In 1948, in an endeavour to devise a simpler method of spinal support, homogeneous inlay grafts of rib were used in the lumbar spine for spondylolisthesis and unstable intervertebral joints.

Ribs, cut into suitable lengths, were placed over the dorsal aspect of the laminæ and sacrum, and held in place by wiring and the pressure of the paraspinal muscles sutured over them. This gave very satisfactory support for a while, the curved portions of the head, neck, and upper part of the shaft adapting admirably to the curvature of the lumbosacral junction.

Although some were permanently successful, these grafts would occasionally soften, and after several years the symptoms would return. The results showed, however, that it was possible to produce spinal support, which would relieve referred pain from overstretching of ligaments merely by placing an inlay over the back of the laminæ and under the paravertebral muscles, thus producing limitation of movement at the affected joint. To obtain more permanent fixation, it was decided to try acrylic inlays.

Acrylic plastic can be inserted in the tissues in a doughy consistence, and it will adapt to local curvatures, hardening in situ within 24 hours. In skull reconstruction such a procedure, over an intact dura, produces a perfect outline.

The use of acrylic inlays which harden in situ is founded upon the experimental work of Blaine (1946a and b), which was adapted to skull reconstruction by Oliver and Blaine (1948).

Acrylic polymer $3^1/_2$ parts, when mixed with acrylic monomer 1 part by volume, forms in a definite time a plastic dough, with an interim stage in which the dough is highly tacky and adhesive. At a temperature of 90°F the dough forms within 15 minutes, and at 80°F within 30 minutes, the time being decreased if the proportion of liquid is reduced. (These figures apply to the 'Kallodent 222' preparation.)

Blaine (1946b) found that such a dough implanted into animal tissues hardens and polymerises within 24–48 hours, the degree of hardness comparing favourably with that of pressure-heated material. The tissue reaction was limited to a fibrous capsule formation similar to that around any non-toxic non-absorbable implant, such as tantalum or polyethylene. Oppenheimer et al. (1953) described tumours around plastic and metallic implants in the rat and mouse after two years, but there are no reports of tumours developing around plastic implants in the goat or man, although experiments have continued for several years. (Dr. J. T. Scales, personal communication.)

In patients in whom acrylic plastic has been used for skull reconstruction, no undue tissue reaction has been observed. In those of the present spinal series in whom the inlay has been exposed, it was found to be surrounded only by a little xanthochromic fluid within a smooth envelope of connective tissue. There seems, therefore, to be no objection to the use of this material, but the tendency to a serous reaction calls for special care when large inlays are inserted.

Method

I have used 'Kallodent 222' in a clear shade. This slow-doughing powder does not generate heat on mixing, and it sets slowly, forming a hard and non-brittle inlay.

The acrylic polymer is sterilised by autoclaving in bottles, or in flat covered metal tins in which it can afterwards be mixed. A plated syringe box is suitable. The polymer, which is a fine granular powder, does not coalesce during sterilisation. The acrylic monomer, after bacterial filtration, is put up in sterile closed capsules, and is highly inflammable. The sterility of both polymer and monomer are checked regularly.

At operation, 20 minutes before the inlay is required, monomer is poured evenly over the polymer in the proportion of 1 part monomer to $3^1/_2$ parts polymer. When the monomer has been absorbed the lid of the container is replaced, and after 20 minutes at operating-room temperature the acrylic mixture will have formed an even plate. The consistence is tested with a spatula. If it is still tacky, further hardening is allowed to take place. It can then be thickened by folding for use in the lumbar region, where inlays of up to $^2/_3$ in. thick are required. In the cervical region $^1/_3$ in. thickness suffices. Finally, an inlay of appropriate size for the cavity exposed is cut from the material, lifted from the box on a broad copper spatula, and, when dry and rubbery, introduced into the wound.

After the insertion of the soft plastic between the lamina and paravertebral muscles, the spine is supported in the optimum position for 24 hours, which allows the inlay to mould snugly over the ridges of the laminæ, producing a well-fitting and firm support.

The incidence of serous effusion around the inlay may be reduced by taking care in preparation to avoid any excess of monomer, and to obtain the correct doughy consistence. If the inlay is inserted when too soft, it is wet with monomer and difficult to handle, tending to become irregular and to form sharp spikes which may irritate the tissues.

Cervical Spine

Immobilisation, support, and rest are the methods of treatment of painful cervical spondylosis most favoured by neurologists. In early cases referred pain may subside quickly after manipulation or immobilisation, but in chronic cases my impression is that those treated by support from a collar obtain the greatest relief, although the stiffness of the neck persists, and they are by no means cured. Some patients can eventually discard their collars, and these are presumably those in whom the

support has allowed joints to stabilise and inflammatory changes to subside. There remain certain patients, however, in whom severe pain persists despite adequate immobilisation. When this pain is the result of nerve-root compression by foraminal osteophytes, decompression by facetectomy (Frykholm 1951, Knight 1958) may give relief. But the nagging, burning ache of referred pain is harder to relieve. In such cases the acrylic inlay may offer permanent relief. The fact that the support is invisible is a considerable advantage to those whose work involves personal contacts or mechanical strain.

Inlays have been inserted in the cervical region to relieve the severe pain sometimes encountered in cervical spondylosis and osteoarthritis, to support chronically painful fracture-dislocations, and for the stabilisation of an atlantoaxial subluxation resulting from rheumatoid arthritis.

The effect is produced by reduction in movement at the level of the painful joint. After operation an extremely good range of spinal movement is provided by the joints above and below the site of immobilisation. But if neck movement is forced beyond this range, putting a strain on the diseased area, a twinge of referred pain is felt, indicating that the diseased joint can still produce pain but is prevented from doing so by the inlay.

All patients are investigated to exclude any compressing lesion associated with the spondylosis—e.g., cord compression produced by spinal bars or arachnoiditis, or root compression produced by intraforaminal osteophytes. If there is no indication for decompression, immobilisation is performed at the appropriate level. Operation is undertaken with the patient sitting up. Through a midline incision the paravertebral muscles are dissected to expose the backs of the laminæ on one side only. It is important not to dissect the muscles over too large an area; the normal muscle attachment should be preserved as far as possible above and below the affected joints to provide a pouch which will retain the inlay. Complete hæmostasis is essential. The inlay must completely fill the space over the laminæ before the paravertebral muscles are resutured to the side of the spine. After wound suture the surface is protected by a covering of gauze and jaconet. A plaster back-slab is applied from the level of the occiput to the scapula, and with the patient upright the head is held in a neutral posture until the plaster sets. It is then bound into place and fixed with strapping. The back-slab is worn for 24 hours whilst the plastic inlay sets and adapts to the curvature of the laminæ. After that period it supports permanently the diseased joints in the required position. The patient is allowed up on the 3rd day, and the stitches are removed on the 6th day. The average patient is fit for discharge within 2 weeks.

Case 1.—A nurse, aged 25, had a long history of brachial neuritis from irritation of the 6th nerve-root by an intervertebral osteophyte. This radicular pain responded to decompression by facetectomy, but after a further strain she developed pain, referred to the shoulder tip and trapezius areas, which proved extremely intractable. She got no relief from repeated manipulation or from wearing a collar, and she was severely handicapped. Since an inlay was inserted over the affected joint she has been able to work, only getting a little aching in the neck at the end of a tiring day. She has discarded the collar, and regards the inlay as " a great success ".

Case 2.—A man of 65, with perhaps the most severe painful cervical osteoarthritis so far encountered, was referred by Mr. Charles Gray. The patient had had pain in the neck since 1955 and lateral flexion was limited. Radiographs showed severe osteoarthritis. A cervicodorsal plastic corset was applied, but this and short-wave diathermy gave no relief.

In October, 1955, severe pain radiated from the right side of his neck to the vertex, to his right shoulder-blade, and to the back and outer border of his right arm. He could not move his neck without pain, and flexion was restricted to 30°. There was evidence of compression of the C6 nerve-root. I decided to attempt surgical treatment. The occipital pain disappeared after occipital neurectomy. Pain in the arm, from nerve-root compression, was relieved by facetectomy, but he was still incapacitated because the slightest movement of his head produced severe pain shooting into the reference areas.

On June 6, 1957, an acrylic inlay was inserted over the laminæ of C4–7 on the right. The day after operation he described the effect as " remarkable ". Within a month he was completely free from pain and had discarded his collar. The range of neck movement had increased, apparently because movements could now be made at healthy joints without exciting movement in the tender areas. At the end of 1958 he still thought the operation was a success; he had no neck pain, and neck movements were free.

Case 3.—This patient's pain was less severe, but was a handicap and annoyance because he could not undertake his normal activities—which included driving long distances, sitting in board meetings, and farming—without constantly wearing a collar. He had had an ache in his neck intermittently for 20 years, but since a motor accident a year previously it had become much more severe. This pain was associated with muscle-spasm in the neck, and it radiated to the midpoint of the cervical spine, to the occiput and between the eyes, and to the trapezius and shoulder tip. There was paræsthesia in the distribution of the C7 dermatome. Neck movement was restricted on the left, and the spine felt " fused " up. Radiographs showed much spondylosis at the C5/6 level. Three times manipulation gave temporary relief for no more than 5 weeks. He was only free of pain when he was passive.

An inlay was inserted over the C4–6 laminæ on the left. 3 weeks after operation he had " nearly 100% movement without pain ", despite much activity. He has continued in comfort without wearing his collar.

Case 4.—A woman of 57 had had rheumatoid arthritis for 8 years. She had been treated by Prof. E. G. L. Bywaters, with improvement in all joints except her neck and elbows. In 1956 undue mobility was seen radiologically at the C1/2 level. In 1958 pain developed in the neck and radiated into the arms, and the subluxation was mobile and palpable inside the mouth; the patient herself felt something in the back of her throat when she swallowed, and a jarring in this region when she walked.

To prevent further subluxation of C1 on C2 (in which C2 moves backwards in relation to the occipital plate), a large acrylic inlay was inserted from the occiput to the level of the C3 lamina, thus holding the 2nd lamina forward in relation to the occiput. The arch of the C1 vertebra was drawn back by silk slings which were tied firmly down below the spine of C2.

After operation a ' Minerva ' plaster collar, with a large window for wound inspection, was applied to encase the head and upper thorax. Extremely careful wound toilet was required in the first 7 days, otherwise the collection of serum around the large inlay might have led to infection. A month later the plaster was replaced by a polyethylene collar and head support. Gentle physiotherapy was given three times a week for 3 months until the collar was discarded. There was then a useful range of rotation of the head, and the patient was free from pain and all unpleasant sensations.

Inlays have been used also to relieve pain associated with old cervical fracture-dislocations. They are most successful when the deformity can be influenced by posture.

In a patient of 58 who had had to wear a collar permanently, an inlay relieved all the deep aching pain, although he still had some pain at the shoulder tips.

A young man, who had previously had radicular pain and muscle cramps in the right arm resulting from vertebral displacement, was given complete relief. $2\frac{1}{2}$ months after operation he took part in winter sports without handicap.

In none of the cases in which small inlays have been inserted in the cervical region has there been trouble from serous reaction.

Lumbar Spine

Acrylic inlays also were employed successfully in patients with the syndrome of low-back pain and referred pain in the legs from overstretching of ligaments produced by abnormal mobility of a lumbar vertebra. In these patients spinal instability was the result of atrophy of a disc, either from injury or degeneration, and there was diminution of an intervertebral joint space radiologically.

When large inlays are inserted in the lumbar region, an excess of fluid may be formed because of the greater surface area of the material. Provided that the fluid is removed by aspiration no harm will result, but if it persists the inlay must be removed before infection occurs. This happened in a few early cases.

If there are signs of root compression, the affected root is exposed by hemilaminectomy. If at operation undue mobility is demonstrated, an acrylic inlay is inserted over the back of the intact laminæ on the side opposite to the hemilaminectomy.

After operation the patient is nursed supine with the spine slightly extended over a pillow for the first 24 hours during which the plastic sets. He is allowed up after 3 days.

I have also inserted inlays after removal of disc protrusions when the preoperative symptoms have suggested instability of the lumbar spine, and abnormal mobility of a vertebra has been demonstrated at operation.

Case 5.—A man aged 62, a school-bus driver, referred by Dr. Francis Bach, had had attacks of lumbar pain and pain in the right buttock for 23 years. On rolling over in bed the pain would wake him. He was forced to sit straight up, and sometimes preferred to stand rather than sit to obtain comfort. Recently the pain had radiated to the right thigh and toes in the distribution of the L4–5 dermatomes. He could only hobble around with the support of furniture.

There was wasting of the right quadriceps and anterior tibial muscle groups. The right knee-jerk and both ankle-jerks were absent. The L4/5 disc space was narrowed. At hemilaminectomy a large protrusion was removed at this level on the right, and an acrylic inlay was inserted in the left. He was discharged, pain free and walking well, 16 days after operation.

A month later he was able to walk about 4 miles; 2 months after operation he painted the ceiling of his home and resumed his previous work.

It seems unlikely that such complete relief of symptoms would have been obtained without this additional stabilisation.

Summary

The use of acrylic plastic, inserted in a "doughy" consistence, and hardening in the tissues within 24 hours, for skull reconstruction has shown that this substance does not provoke significant tissue reaction.

A similar method has been used for spinal stabilisation. A sheet of soft acrylic plastic inserted between the lamina and paravertebral muscles, which hardens and adapts to the local curvatures within 24 hours, produces an efficient support for that area of the spine.

Such inlays have proved successful in patients with chronic referred pain resulting from cervical arthritis, spondylosis, or injury, who had previously had to wear a collar constantly, and in some patients who had had incapacitating low-back pain and referred pain in the legs for many years because of unstable joints in the lumbar spine.

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PROPHYLAXIS OF ISCHÆMIC HEART-DISEASE BY THYROID THERAPY

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BEFORE Strisower et al. (1957) suggested the use of dried thyroid as a prophylactic against coronary heart-disease, Barnes and Barnes (1957) had submitted a preliminary report on this subject. Nine years have elapsed since this work was undertaken, and I give here an interval progress report. Reports on association of thyroid deficiency with arteriosclerosis (see Kountz 1951) may be summarised briefly as follows:

1. Thyroidectomy in some species is followed by generalised atherosclerosis.

2. Excessive cholesterol administration will cause atherosclerosis in some species. This effect is enhanced by thyroidectomy and is prevented by simultaneously administered thyroid.

3. Spontaneous or surgical myxœdema is commonly associated with severe arteriosclerosis.

4. No degenerative arterial changes are found in Graves' disease.

Hypercholesterolæmia has been consistently found in association with myocardial infarction all over the world in recent years. This association has been known since Hurxthal's (1934) demonstration that within limits the blood-cholesterol reflects thyroid activity. Thyroid deficiency is accompanied by elevated cholesterol levels while in hyperthyroidism the cholesterol level is below normal.

Since I had spent thirty years investigating thyroid deficiencies, it was natural that I began looking for hypothyroidism in cases of hypercholesterolæmia. It soon became evident that in most cases of elevated blood-cholesterol there were some symptoms, signs, or laboratory findings consistent with subnormal thyroid function. A long-term study was then undertaken to see if (*a*) thyroid therapy would control hypercholesterolæmia before evidence of arteriosclerosis was detectable, (*b*) thyroid therapy would benefit patients who had already suffered myocardial infarction, (*c*) the incidence of arteriosclerosis could be reduced by long-term therapy. Sufficient time has elapsed to answer the first question. Treatment of cases with myocardial infarction is encouraging and deserves further trials. Another fifteen to thirty years will be necessary to establish whether arteriosclerosis can be prevented.

Methods

Approximately 700 patients from a private general practice were the subjects for this investigation. New cases are being added continually. They were unselected by me but may not exactly represent a cross-section of our population: because I have recognised and treated thyroid deficiencies for many years, a slightly higher percentage of thyroid deficiencies may have accumulated in my practice than is present in the general population. The patients were adults ranging in age from 20 to 100 years.

Investigation of a new patient included history, physical examination, urinalysis, chest X-ray, electrocardiography, blood-count, erythrocyte-sedimentation rate, and blood sugar, creatinine, and cholesterol. Recently blood coagulation-time by the Lee-White method has been added. These investigations are repeated annually in all cases where feasible, and at two or three year intervals in others. Cholesterol was estimated photometrically after extracting either whole blood or serum overnight with alcohol-ether mixture. Since the cholesterol content of serum is higher than that of cells, the initial

values before treatment were higher for serum. After treatment, as the serum-cholesterol is reduced the whole-blood and serum values come closer together.

80 patients who had a blood-cholesterol over 200 mg. per 100 ml. were selected for therapy. Although many workers consider this level within the normal range, coronary-artery occlusion sometimes develops with values near 200 mg. If cholesterol is a factor in arterial degeneration, we must reduce the blood-level below 200 mg. to be safe in all cases. Further, it was soon found that thyroid therapy would reduce hypercholesterolæmia to values below 200 mg. without any evidence of hyperthyroidism. As soon as a blood-cholesterol was found above 200 mg., either at the initial or subsequent examinations, the patient was put on desiccated thyroid. No advantage has been found for the more expensive preparations with thyroid-like activity. The dosage has varied from 65 mg. (gr. 1) to 260 mg. (gr. 4) daily, 130 mg. (gr. 2) being the most usual. The cholesterol level was checked again in two or three months, and, if it was still above 200 mg. per 100 ml., the thyroid dosage was increased. Once a satisfactory level was attained, the

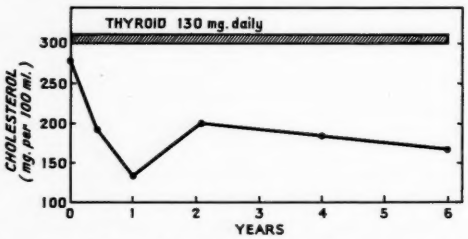

Fig. 1—Effect of thyroid therapy on raised blood-cholesterol level.

dosage was not altered for a year. Some patients have continued the same dosage for eight years.

In all cases some evidence could be found in the history or the physical or laboratory data for hypothyroidism. Basal temperatures were uniformly low, and they have been used as a guide for dosage (Barnes 1942). The minimum dose that would relieve the patient of symptoms and reduce the blood-cholesterol was employed. In no case has the basal temperature exceeded the normal range, nor have symptoms of hyperthyroidism appeared. It has been necessary to discontinue medication in only 1 case—a severe diabetic, who became weak during thyroid therapy.

Results

The initial blood-cholesterol levels of patients put on thyroid therapy ranged from 200 (the arbitrary lower limit) to 381 mg. per 100 ml. The average was 242 mg. The patients' ages ranged from 32 to 79 and averaged 45. A typical response to treatment is shown in fig. 1.

Fig. 1 shows that the blood-cholesterol level, initially 274 mg., promptly fell below 200 mg. when thyroid therapy was started. This patient was 59 years old when treatment was started, and his dosage has remained at 130 mg. of thyroid daily during the past seven years.

The average blood-cholesterol for the 80 patients after treatment was 180 mg. with a range of 147–241 mg. In only 5 cases did the level not fall below 200 mg., and

TABLE I—EFFECT OF THYROID THERAPY ON 80 CASES OF HYPERCHOLESTEROLÆMIA

Cholesterol range (mg. per 100 ml.)	No. of patients	Average cholesterol (mg. per 100 ml.)	
		Before	After
200–219	36	211	174
220–239	14	232	181
240–259	12	247	181
260–279	7	269	175
280–299	6	289	179
300–up	5	362	203

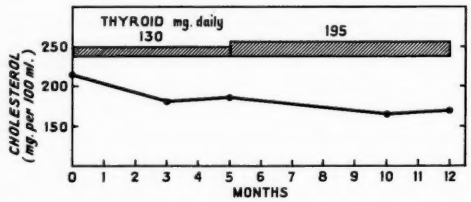

Fig. 2—Effect of thyroid therapy on blood-cholesterol level in a case of myocardial infarction.

I believe that these levels will decrease further with time. The duration of treatment has been short, and new values are not available after the dosage of thyroid was increased. Table I summarises the results on the 80 patients.

Thyroid therapy reduced the average blood-cholesterol to approximately the group average of 180 mg. per 100 ml. per 100 ml. The average for the 5 patients in this group was 203 mg., but in only 1 case did the level fail to fall below 200 mg. This patient had an initial level of 360 mg. During two months of treatment on 130 mg. of thyroid daily, the cholesterol fell to 241 mg. but further observations could not be made since he moved to another State.

The success in controlling hypercholesterolæmia with thyroid led to a trial of the same therapy in cases of myocardial infarction. 4 cases in the present series have been followed. The result in 1 case is shown in fig. 2.

The blood-cholesterol level, initially 213 mg. per 100 ml., promptly fell, and has been maintained for three years well below 200 mg. per 100 ml Since this patient was overweight he was put on a high-fat, low-carbohydrate diet for reducing Such a diet has been successfully used for sixteen years (Barnes and Keeton 1941) The daily intake of fat was over 50% of the calories, and included eggs, bacon, butter, salad dressings, and fat meat. No effort was made to use unsaturated vegetable

TABLE II—EFFECT OF THYROID THERAPY ON CHOLESTEROL OF PATIENTS WITH MYOCARDIAL INFARCTION

Case	Ag (yr.)	Cholesterol (mg. per 100 ml.)		Duration of treatment (yr.)	Remarks
		Before	After		
A	39	375	190	3	Alive and well
B	48	213	157	4	Alive and well
C	59	—	157	9	Alive and well
D	70	201	173	1½	Died with stroke and second coronary thrombosis

fat. The drop in cholesterol was not due to weight loss since the cholesterol remained low, but the weight went up during the next year. The results in all 4 cases are summarised in table II.

Sufficient time has not elapsed for significant observations on the incidence of arteriosclerosis in the treated group. Myocardial infarction has not occurred in any of the cases where the cholesterol has been lowered over any length of time. Twenty years from now more information will be available on this question.

Discussion

The striking reduction in blood-cholesterol illustrated in fig. 1 and observed in all of the 80 cases included in table I leaves no doubt about the efficacy of thyroid therapy. Here is a simple, inexpensive method of reducing hypercholesterolæmia, and maintaining normal cholesterol values for indefinite periods.

Fortunately long-continued thyroid therapy, which is

often necessary, is harmless. Murray's (1920) original case of myxœdema required treatment continually for the remaining 28 years of her life after the disease was recognised; the patient died at the age of 72. In a reported case medication was continued for over 50 years. I have personally observed several thousand cases, some of them under continuous treatment for 20 years, and have not seen any untoward symptoms develop unless excessive doses were administered. The basal temperature (Barnes 1942) serves as an excellent guide to dosage.

Some clinicians are reluctant to administer thyroid, and consider it dangerous. Careful search of the literature indicates that such an opinion could arise only from a series of reports between 1925 and 1938. 8 deaths were reported in cases of myxœdematous heart-disease during or after thyroid therapy. Scrutiny of the protocols reveals two outstanding facts: (*a*) these patients suffered from far advanced arteriosclerotic heart-disease before therapy was started, and (*b*) huge doses of thyroid were administered.

There is very little evidence that therapeutic doses of thyroid are harmful. Christian (1925) reported the first series of 6 cases of myxœdematous heart-disease. 1 of the 6 patients died before any therapy was started, illustrating that one must be cautious about condemning any medication in this disorder. 4 improved on thyroid therapy despite a dosage of 390 mg. (gr. 6) daily (it was later found that the maintenance dose was 130 mg. (gr. 2) daily). 1, with a history of angina for 4 years, was treated with 520 mg. (gr. 8) of thyroid daily; congestive failure developed and the patient died in a short time. It seems more logical to blame the massive dosage rather than the drug itself.

Although Sturgis and Whiting pointed out in 1925 that it was advisable to treat myxœdematous hearts with small doses of thyroid and gradually increase the dose, their warning was overlooked by several investigators during the next 15 years. 7 more deaths were reported. In each instance the patient was either in poor clinical condition at the start of therapy or an overdose was used. One 30-year-old man was given 970 mg. (gr. 15) daily with disastrous results.

Wallach et al. (1958) confirm older reports that even aged patients with advanced arteriosclerosis can tolerate necessary thyroid therapy, if the dosage is initially small and is gradually increased.

The excellent work of Kountz (1951) leaves no doubt that thyroid therapy is indicated even in advanced arteriosclerosis. In 280 cases, some kept as untreated controls, thyroid therapy decreased vascular accidents as well as mortality over a 5-year period. Kountz gave a small initial dose and gradually increased it. The evidence seems conclusive that thyroid is not a dangerous drug and can be used effectively in therapeutic dosage whereever indicated.

In addition to reducing hypercholesterolæmia, thyroid therapy has other physiological actions that might benefit arteriosclerosis. The circulation-time is prolonged in myxœdema but can be restored to normal promptly with thyroid. Stagnation of blood would facilitate thrombosis. Further, a few cases of hypothyroidism have an accelerated clotting-time by the Lee-White method. This has been investigated during the past year, and in cases where the coagulation-time was short it has been restored to normal by thyroid therapy. Finally, blood-flow through the coronary arteries is affected by thyroid function. Leight et al. (1956) reported an increase of coronary flow in hyperthyroidism. This was confirmed by Rowe et al. (1956), who also found that thyroidectomy increased coronary vascular resistance. These observations indicate that there is a decrease in blood-flow through the coronary arteries in thyroid deficiency. Such a condition would facilitate myocardial infarction and angina pectoris.

Appararently thyroid therapy increases the coronary blood-flow in cases of myocardial infarction. Lerman and White (1946) found that angina disappeared in all but 2 cases of their series. They reported 28 cases of coronary-artery disease occurring before the age of 40. In general the metabolism was low and the cholesterol was high. Thyroid therapy increased the metabolism, and lowered the cholesterol. In those patients free of angina before therapy, pain did not develop. Apparently the increase in blood-flow to the myocardium more than compensated for the additional work of the heart. Lerman and White were using very small doses of thyroid (personal communication), and after a few weeks the cholesterol levels began to rise again. For this reason they abandoned further thyroid therapy.

The results illustrated in fig. 2 and table II clearly show that thyroid therapy will reduce raised cholesterol levels in myocardial infarction to normal and maintain them at normal for years.

It is known that the body can compensate for small doses of thyroid, and apparently this happened in the cases of Lerman and White (1946). It is apparent that the larger doses reported here were effective for indefinite periods without causing harmful effects. In fact, in the case illustrated in fig. 2, the patient had angina following his myocardial infarction until thyroid therapy was instituted. After that time he could do more work and be entirely free from angina. The other cases represented in table II did not have angina either before or after thyroid therapy. All 4 patients felt much better. Although case D died $1^1/_2$ years after his initial attack from a stroke and a second coronary thrombosis, he felt well and worked in an insurance office during the last year of his life. Since he was 70 years old at the time of his initial attack, it is not surprising that he lived only $1^1/_2$ years more. The other 3 patients have continued at their usual occupations since recovery from their first myocardial infarctions. They have not been on anticoagulant therapy since they recovered from their initial attack, and all of them are eating unrestricted diets containing animal fats. Apparently the thyroid therapy has not only reduced their cholesterols, but has also increased their coronary circulation.

It is too early to tell whether the development of arteriosclerosis can be prevented, but this seems a most important question to investigate. If we are to stop the ravage of coronary-artery disease, therapy must be begun long before myocardial infarction. Since the cholesterol level is raised in cases of myocardial infarction, certainly treating all cases of hypercholesterolæmia would reach those in whom arteriosclerosis is developing. This will entail several years of observation, but on theoretical grounds it offers the most promising lead at the present time. Our attention must be focused on younger individuals with hypercholesterolæmia before arteriosclerosis has advanced to an irreversible degree.

Although other means of reducing hypercholesterolæmia have been described, none of them is as effective as thyroid therapy. Further, increase in coronary blood-flow, as mentioned above, may be of greater importance than

the reduction of the cholesterol. The rapid development of arteriosclerosis in the athyroid human (Fishberg 1924) leaves little doubt that the thyroid deficiency is an important factor. Whether the effect is produced by hypercholesterolæmia, by a decrease in coronary circulation, or by some other pathological process favouring the development of arteriosclerosis must be answered by further studies.

Summary

In the past nine years, 80 cases of hypercholesterolæmia have been selected for study from 700 apparently normal adults in a general practice. Evidence for hypothyroidism was found in the history, the physical examination, or the laboratory data.

Thyroid therapy reduced the average blood-cholesterol from 242 mg. to 180 mg. per 100 ml. No evidence of hyperthyroidism was found.

4 cases of myocardial infarction were treated with thyroid. Their cholesterol levels fell below 200 mg. per 100 ml., and their clinical conditions were improved.

Published reports indicate that alleged damage to the heart during thyroid therapy was due to severe overdosage.

Small doses of thyroid greatly benefit cases of severe arteriosclerotic heart-disease.

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PSYCHOSIS AND ADDICTION TO PHENMETRAZINE (PRELUDIN)

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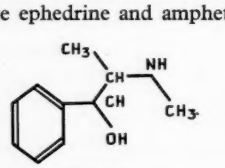
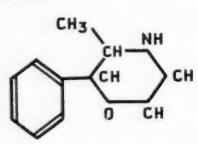
PHENMETRAZINE ('Preludin'), a sympathomimetic drug discovered by Thomae and Wick, was first used in 1954 in the treatment of obesity. Since then it has been given in asthma, in parkinsonism, and as a euphoriant.

Preludin is an oxazine derivative and has a structure not unlike ephedrine and amphetamine:



Ephedrine



Preludin

Its action is similar to that of amphetamine. Therefore, when cases of psychosis and addiction due to preludin were reported by Bethell (1957), Clein (1957), Lubenthal (1957), and others, it was not surprising that they were similar to cases of amphetamine psychosis and addiction reported by Connell (1958), Herman and Nagler (1954), and Hara et al. (1954).

I supposed the condition to be rare, but within six months I saw no fewer than sixteen patients who had taken preludin and had become ill. Twelve of these had a psychotic disturbance.

Case-histories of three patients are given below. Tables I and II containing personal data and clinical features of the twelve psychotic patients are given for easy comparison.

Case-reports

Case 1.—Woman, aged 33, cohabiting. For three years before admission she took preludin tablets because she felt dull and lacking in energy when she stopped taking them.

About a month before admission she felt depressed and took 60 preludin tablets one day. Within a few hours she became hallucinated, hearing fairground music, the sound of the baby crying, and her "husband's" voice. Her disturbance cleared about a week after admission to hospital. Two weeks later after discharge she was again taking 8–9 preludin tablets a day and hallucinations reappeared. She heard cars driving up at night and stopping outside her house. She heard church bells ringing and even in a crowd she would hear voices coming from over their heads. She listened intently to see if they belonged to people who were dead, for she thought they came from another world. A man's deep voice was heard saying that she was going to die. As a result she handed her baby to the police and asked them to care for it.

In the two days before admission she took 30–40 tablets of preludin and her distress became worse. She thought that her end was near and consulted a doctor who arranged her admission to St. Francis' observation ward.

On admission she was agitated and apprehensive to a degree that prevented extensive physical examination. She was dirty and her clothes were in poor condition. Her speech was very rapid and rambling. She was frightened and cried at times. She was deluded, stating that preludin tablets had stuck in her throat, that she was going to die as a result, and that her husband was also going to die, for he had had visions. Her memory was good and no disturbance of level of consciousness was noted.

Two days later she was more composed and cooperative but showed some lability of mood. Her talk was now normal apart from a tendency to ramble. Orientation and memory were satisfactory.

Complete recovery from delusions and hallucinations did not occur for one week and marked emotional lability was present until her discharge on the twelfth day. She resumed taking preludin tablets soon after discharge and has had two further admissions.

Case 2.—Woman, aged 26, single. After taking up to 6 'Benzedrine' tablets a day for six years, the patient started taking preludin tablets in 1955, increasing to 10–15 tablets a day.

Six months before admission a love affair was broken off. As a result, she became depressed, felt like committing suicide, and did not go to work. Preludin consumption increased, temporarily to 20 tablets a day, later returning to 10–15 a day. Some nights she felt her ex-lover was outside the door; she would think he had knocked, and on looking through the keyhole, that his lighted cigarette could be seen. After a month, she improved and returned to her work.

A fortnight before admission, her job as a journalist ended. Her brother noticed that she was writing many letters including abusive and vulgar ones to her ex-lover. A few days later she asked her mother if anyone had knocked on the door, as she believed the Nazis were coming to kill her. She felt that the telephones were tapped and neighbours spying on her. She blocked up the windows, put furniture against the doors, and peeped through the keyholes. Things were noticed outside the window at night. A man was seen on the roof of the house opposite and in her room, "moving things" which she chased

TABLE I—PERSONAL DATA

Case no.	Age	Sex	Status	Occupation	Previous mental illness	Other drugs taken	Reason for starting Preludin	Introduced by	Duration of Preludin	Believed max. daily dose
1	33	F	s. cohabiting	Housework	None	None	Relief of depression	Doctor	3 years	60 tabs.
2	26	F	s.	Journalist	None	Amphetamine	Stimulant	Doctor	3 years	20 tabs.
3	31	F	s.	Nurse	None	Amphetamine, alcohol	Stimulant on night duty	Nurse	4 months	20 tabs.
4	33	F	Divorced, cohabiting	Unemployed	Alcoholism	Dexedrine, s. amytal, persomnia	Slimming	Friend	1 year	60 tabs.
5	33	F	s.	Bus conductress	Amphetamine psychosis × 2	Amphetamine	Stimulant	Pharmacist	4 weeks	16 tabs.
6	19	M	s.	Merchant navy seaman	None	None	Stimulant	Friend	6 days	30 tabs. in 6 days
7	51	F	s.	Domestic	Alcoholic depression, suicide attempt	Alcohol	Relief of depression	Preludin addict	2 years	40 tabs.
8	24	F	s.	Typist (unemployed)	None	Amphetamine (normal doses)	Stimulant, slimming	Friend	18 months	20 tabs.
9	24	F	s.	Actress	Depression	Alcohol	Slimming	Friend	18 months	40 tabs.
10	28	F	M.	Bus conductress	None	None	Stimulant	Chemist	2 years	4 tabs.
11	26	F	s.	Consumer research	None	Dexedrine	Stimulant	Friend	18 months	40 tabs.
12	26	M	s.	Night club porter	None	Marihuana, aspirin, "ganjers"	Stimulant	Friend	4 months	40 tabs.

with a stick. At times she heard guitar music and hands tapping on the window. On the day before admission she decided to buy a wedding ring. At the first shop no ring would fit her, but at a second shop 200 yards away there was a ring which fitted. In her eyes, this showed that some organisation, probably the Communist Party, was helping her. On her arrival home she was extremely restless, and claimed that she had married her ex-lover. As a result of her condition she was admitted to St. Francis' observation ward.

Physical examination revealed scabies. Mental examination revealed a fully cooperative cheerful woman whose speech was normal. She claimed insight into her delusions and said they were a result of her imagination due to abuse of preludin.

This picture did not last. She became impulsive and overactive in the ward, attacking one of the staff. Her hallucinations returned for one night and fresh delusions appeared. She felt that she was going to be brainwashed and converted to Communism, that her doctor was hypnotising her, that scratch marks on her arm were to test the depth of hypnosis. Slight pressure of talk was present and she was emotionally labile, often elated. No fluctuation in level of consciousness as judged by orientation and clinical impression was seen.

Recovery was slow and insight into her delusions came and went. After three months she appeared to be free of psychotic symptoms.

Case 8.—Woman, aged 24, single. In July, 1957, she was introduced to preludin by a friend who recommended it for slimming. She took the tablets in increasing doses so that at the time of admission (in November, 1957) she was consuming 15–20 tablets a day, although she said that they had no effect on her, and she did not know why she took them. About fifteen months before admission the patient had become interested in religion. This interest dominated her conversation for three months before admission. At the same time the mild feelings of depression lifted. She declared that she had

TABLE II—CLINICAL DATA

Case no.	Motor activity	Pressure of talk	Mood	Ideas of reference and delusions	Hallucinations				Disorientation	Duration of symptoms
					Visual	Auditory	Olfactory	Tactile		
1	No change	Increased	Fearful, anxious, depressed	Nihilistic delusions	−	+	−	−	−	7 days
2	Increased, restless	Increased	Elated, labile	Paranoid delusion, ideas of reference	+	+	−	−	−	3 months
3	Diminished	Diminished	Suspicious, hostile	Paranoid delusions, ideas of reference	+	+	−	+	−	1 week
4	Agitated, restless	Increased	Depressed, anxious, panic attacks	Depressive delusions	−	−	+	−	−	Days
5	Increased	Increased	Anxious, fearful	Paranoid delusions	−	+	−	−	−	Few days
6	Increased	Increased	Excitement	Delusions, ideas of reference	−	+	−	−	Time and place	2 days
7	Agitated	..	Depressed	Depressive delusions	−	+	−	−	−	Days
8	Increased	Increased	Elated	Delusions of grandeur	−	+	−	−	−	6 weeks
9	Diminished	None	Depression	Paranoid delusions	+	+	−	−	−	5 weeks
10	Diminished	None	Depression	Paranoid delusions	−	+	−	−	−	9 weeks
11	..	None	Suspicious	Paranoid delusions, ideas of influence	−	−	−	−	−	5 weeks
12	Diminished	None	Anxiety	Paranoid delusions	+	+	−	−	Time	3 days

given herself to God and until he gave her back she was the vehicle of other people, and a living sacrifice for God. She became so restless and excited that she was admitted to an observation ward. On examination she was cheerful and elated, talking at length and in a rambling fashion. Two weeks later her condition was satisfactory but she remained elated and still dwelt on religious topics. Her second, third, and fourth admissions were preceded again by intermittent consumption of large doses of preludin—usually 20 at a time.

On her fourth admission she had become deluded and hallucinated again. Mood was elated. There was marked disorder of sequence in thinking—e.g., " God has to obey the Queen. Dreadful for us, but the whole world would know. For England is the mother country and they all come out of her." This type of thinking did not appear in other patients. Her disturbance persisted for six weeks.

Discussion

The twelve patients with a psychosis may be considered in two groups.

The first group consists of patients 1, 3–7, and 12 whose symptoms were indistinguishable from those of an amphetamine psychosis. They had an illness in which delusions of a paranoid, nihilistic, and depressive type occurred, together with hallucinations and disturbance of affect. Behaviour was altered: some were restless and agitated. No thought disorder typical of schizophrenia was elicited. Disorientation was found in two cases only. All recovered within a week. Patients 1, 4, 5, and 8 relapsed as a result of taking preludin again. Similar cases have been reported by Bethell (1957), Brandau (1958), Lubenthal (1957), and others. The history of excessive intake of preludin, a frank psychosis and its rapid resolution on stopping the drug, justifies the term psychosis due to preludin.

The second group, patients 2 and 8–11 had a delayed recovery. All (except case 10) had taken preludin for months—10–20 or more tablets a day for several weeks. The symptoms differed slightly from the first group in so far as cases 2 and 8 were elated and more active. Cases 8 and 9 had definite schizophrenic thought disorder with vagueness, overinclusiveness, and bizarre associations.

It is possible that the psychosis coincided by chance with taking preludin. It is also possible that the patients were taking preludin to alleviate early symptoms of psychosis—though it is improbable that these symptoms could be suppressed for such a long time. Despite close supervision patients may have continued to take the drug while in an observation ward, thereby prolonging the psychosis, but this is unlikely. This could not be excluded, however, because a biochemical test for preludin has not been developed. There remains the likelihood that large doses of preludin can cause a psychotic schizophrenic type of illness lasting weeks or months. As with amphetamine psychosis, in cases of delayed recovery the clinical picture was of a schizophrenic psychosis.

Background and Personality

Excluding patient no. 7 (a woman of 51) the patients were aged between 19 and 33. Eleven out of the sixteen were women. All but one were single or divorced. Their work record was unstable as thirteen had changed jobs frequently. Thirteen had taken drugs, alcohol, or amphetamine derivatives in the past. Five had had a severely disturbed upbringing. None had paranoid traits when well. Four were extroverts. Thus the impression emerges that this group resembles other drug addicts.

Drug Data

Drug addicts are well known for their capacity to lie about the amount of drugs taken. Some of my patients denied taking preludin when first questioned and many admitted later that they had taken more than they had said at first. A number had taken preludin for slimming and had then noticed its stimulant effect. This may account for the preponderance of females. Others had taken it as a " pep " pill. All had found that the number of tablets taken had to be increased in order to obtain the same effects. Excluding the subacute intoxication, all the patients except one had taken over 10 tablets a day for many weeks. The amount taken did not appear to have a close relation to the severity of the illness. Withdrawal symptoms were not common, but patients 3 and 8–10 had depression and marked lethargy for some days whereas patient 1 had lability of mood; only two asked for further preludin. At home, however, they had difficulty in refraining from taking preludin. The after-effects of let-down, depression, or fatigue made them take more.

In 1957 the Pharmaceutical Society advised pharmacists not to dispense preludin except on doctors' prescriptions. However, none of our patients had had much difficulty in getting the tablets.

Diagnosis

The diagnosis of any illness depends on awareness of its existence, and Connell (1958) pointed out that many amphetamine psychoses were missed for this reason. This applies equally in the diagnosis of addiction and psychosis due to preludin. As amphetamine-like drugs are now listed as Schedule IV Poisons, they are more difficult to obtain and it is likely that many people who have used amphetamine derivatives in the past will turn to other drugs, and preludin psychosis will increase.

At present a history of taking preludin is necessary for diagnosis, for no satisfactory biochemical test exists. The initial story from the patient should not be accepted as reliable; for some will deny taking tablets at first and admit it later. In all cases mood is disturbed. The majority are anxious, depressed, or frightened. There is no flattening or incongruity of affect. Two patients who had a delayed recovery were elated. Delusions and hallucinations, sometimes visual, are common. Pressure of talk is frequent but not invariable. Schizophrenic type of thought disorder is uncommon. Disorientation may occur. Clouding of consciousness is difficult to assess, but I found no obvious signs. However, these patients were usually not examined late at night—the time when many complained of an exacerbation of their symptoms. Fatigue on withdrawal of the drug may be present. Any physical signs of sympathetic activity present due to preludin cannot be distinguished from those due to anxiety. A final important feature in the diagnosis is the rapid recovery after the drug has been withdrawn.

If consumption of preludin is concealed, psychosis due to preludin cannot be differentiated from other psychoses. As with amphetamine, some cases of psychosis associated with preludin intake have been eventually labelled schizophrenia. Whether abuse of the drug caused schizophrenia or was merely a symptom of the illness remains undecided.

Control of Preludin

Apart from the cases of psychosis already described, I have seen four others of excessive consumption. All had disturbed behaviour resulting in admission to a mental ward.

Preludin was taken by the patients to "pep" them up, combat depression, or restore energy. To maintain this effect, increasing doses were taken, sometimes resulting in a psychotic episode. In one case seen by me and in two cases reported by Seager and Foster (1958), work and social capacity had become disturbed even to the point of stealing money to obtain preludin. Three patients stated that in certain coffee bars and clubs in London, preludin is used frequently as a pep tablet. On stopping preludin in hospital, four showed marked fatigue and tiredness—two demanding more preludin.

The prospect of increasing abuse of preludin raises the question of how much control of this drug there should be.

The World Health Organisation (1950) and the Drug-Addiction Committee of the American National Research Council have defined addiction as "a state of periodic or chronic intoxication detrimental to the individual and to society, produced by the repeated consumption of the drug (natural or synthetic). Its characteristics include: (1) an overwhelming desire to continue taking the drug and to obtain it by any means; (2) a tendency to increase the dose; (3) a psychological and physical dependence on the effects of the drug." Isbell and Fraser (1950), in an extensive review of addiction, disagree with the inclusion of the term "dependence" as an essential part of addiction. Satisfactory as the definition is to the pharmacologist, the clinician is concerned with possible harm to an individual or society from a drug. Dependence is important mainly because it causes addiction to be continuous rather than periodic. Rigid adherence to the term "dependence" prevents the inclusion of cocaine and marihuana as addiction-producing drugs. Because of its social consequences, preludin should be defined as a drug of addiction for the same reasons as are cocaine and marihuana and should be placed on the list of Schedule IV Poisons of the Pharmacy and Poisons Act, 1933.

Summary

Preludin, a drug similar to amphetamine and ephedrine, is a sympathomimetic agent with euphoriant stimulating qualities.

Twelve cases are reported in which there was addiction to this drug, producing a psychotic illness. The clinical picture cannot be distinguished from amphetamine or bromide psychosis, or alcoholic hallucinosis. Restlessness, pressure of talk, disturbance of mood, delusions, and hallucinations are present, without clouding of consciousness. Preludin should be made a Schedule IV Poison so that its abuse can be prevented.

The advice and helpful comments of Sir Aubrey Lewis and the late Dr. A. Harris are gratefully acknowledged.

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THE CAUSATION OF HERNIÆ BY WEIGHT-LIFTING

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LIFTING a heavy weight is a well-known cause of hernia of the anterior abdominal wall and prolapse of pelvic viscera, and the immediate cause seems to be a rise in intra-abdominal pressure. A raised intra-abdominal pressure must act equally in all directions within the cavity, and it is surprising that the onset of diaphragmatic herniation is rarely associated with weight-lifting (Edmunds 1957). Barrett (1952) and Bourne (1952), however, have suggested that the stomach might none the less be forced into the chest by pressure differences across the diaphragm, and if this is so it suggests that there is but little difference in intrathoracic and intra-abdominal pressure when heavy weights are lifted. That there is indeed a change in intrathoracic pressure during weight-lifting is suggested by the suppressed grunt or gasp which frequently accompanies such activity.

Davis (1956) and Bartelink (1957) have measured the changes in intra-abdominal pressure during weight-lifting, finding very little change in pressure when upright, but a considerable increase when stooping. Davis described this increase as consisting of an abrupt large rise, the *snatch* pressure, followed by a lower but sustained increase in pressure, the *lift* pressure (fig. 1). Bartelink believed that the lift pressure decreased when the weight was held for a long time, but his evidence is inconclusive.

The experiments described here are partly an amplification of previous work on intra-abdominal pressure changes during weight-lifting, with additional observations on changes in intrathoracic pressure during this activity.

Method

Observations were made on 5 healthy adult males aged 21, 21, 24, 34, and 39 years.

Pressures were measured by placing thin-walled rubber balloons in the œsophagus, stomach, and/or rectum, and connecting these to rubber-diaphragm tambours, which in turn recorded by styles on smoked drums or by light pens on paper records. Œsophageal balloons were of 10 ml. capacity, the others of 20 ml. After insertion the position of the balloons was checked by observing the pressure changes during deep breathing and during Muller's manœuvre. The subjects were asked to lift series of weights in the erect position, while stooping, and while supported by their legs face downwards with the trunk horizontal (the "prone" position).

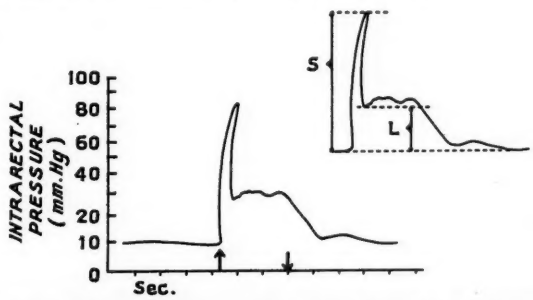

Fig. 1—Rectal pressure tracing from subject lifting 20 kg. in stooping position. Method of measuring snatch (S) and lift (L) pressures is indicated. Weight lifted at the first arrow and replaced at second.

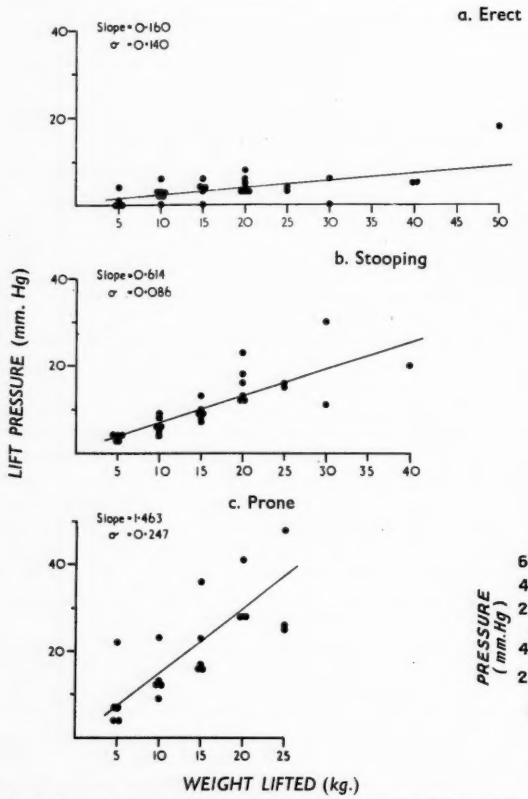

Fig. 2—Intra-abdominal lift pressures recorded in 5 subjects while lifting increasingly heavy weights in (a) erect, (b) stooping, and (c) prone positions. Regression data are given; apparent increase in pressure with increasing weight in the erect posture is not significant, whereas difference between slopes in each of the three positions is significant.

All 5 subjects lifted increasingly heavy weights in each of the three positions while intra-abdominal pressures were recorded, 2 subjects repeating the experiments while simultaneous intra-abdominal and intrathoracic recordings were made. The weights employed consisted of series of 5 kg. lead blocks which could be attached to handles in such a way that the weight was always equally distributed between the two hands. In a third series of experiments 2 subjects repeatedly lifted a 20 kg. weight with increasing rapidity through a vertical distance of 20 cm. while recordings were made of the intrarectal pressure and the time required for the lift.

The snatch and lift pressures were then measured from the records, tabulated, and expressed graphically.

MEANS AND RANGES OF INTRA-ABDOMINAL LIFT PRESSURES (MM.HG) IN 5 YOUNG MALE ADULTS HOLDING WEIGHTS AGAINST GRAVITY IN THREE POSITIONS

Weight held (kg.)	Erect			Stooping			Prone		
	Lift pressure		No. of observations	Lift pressure		No. of observations	Lift pressure		No. of observations
	Mean	Range		Mean	Range		Mean	Range	
5	1	0–4	7	4	3– 4	6	11	4–22	6
10	3	0–6	8	6	4– 9	6	16	9–23	6
15	3	0–6	6	10	7–13	7	24	16–36	6
20	5	3–8	8	16	11–23	6	32	25–41	3
25	4	3–4	3	16	15–18	3	34	26–48	4
30	3	0–6	2	21	12–30	2	..	..	..
35	5	..	1	..	..	..	..	..	..
40	5	..	1	20	..	1	..	..	..
50	17	..	1	..	..	..	..	..	..

Results

INTRA-ABDOMINAL PRESSURE

Effect of Position

Snatch pressures occurred 51 times in the 84 individual tests performed in the three positions, but did not seem to be more common in any one position. They showed considerable variation between different individuals, and in the same individual when experiments were repeated. Although the speed of lift was not recorded in this first series, the snatch pressures appeared to occur most frequently when the weights were lifted rapidly.

Lift pressures (fig. 2a) occurred in some of the experiments in the upright position, but these increases were small, and were not constant between different individuals or in the same individual when tests were repeated.

In the stooping position (fig. 2b) a considerable, significant rise in the lift pressure was observed in all 5 subjects, even when the weight was as small as 5 kg. In the prone position (fig. 2c) the lift pressures obtained from a given individual for a given weight were always greater than those obtained in the same subject in the stooping position.

Effect of Increasing Weight

In the upright position, increasing the weight from 5 up to 40 kg. caused no significant increase in intra-abdominal pressure. In the stooping position increasing the weight caused an increase in the lift pressure obtained, and usually an increase in the snatch pressure (see table).

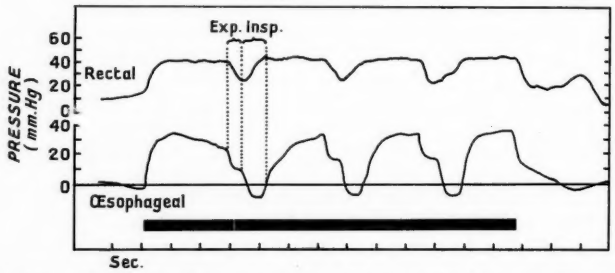

Fig. 3—Simultaneous recordings of intrarectal and intraœsophageal pressure changes while holding weight against gravity in stooping position. Changes during expiration (exp.) and inspiration (insp.) are indicated. Black line shows time for which weight was held.

Similarly in the prone position increasing the weight increased the lift pressure. The highest pressures were recorded in this position; lifts of 25 kg. resulting in snatch pressures of over 70 mm. Hg, and lift pressures of up to 48 mm. Hg.

INTRATHORACIC AND INTRA-ABDOMINAL PRESSURES

2 subjects, with intrarectal and intraœsophageal balloons in situ, lifted increasingly heavy series of weights in the stooping position, and repeated this on a second occasion.

With small weights (up to 10 kg.) lifted slowly, there was an intra-abdominal lift pressure as before. A pressure increase of a similar order occurred in the thorax except during inspiration, when the thoracic pressure fell to a negative value. With larger weights it was found that a deep inspiration preceded the lift; lifting the weight induced a thoracic lift pressure which was equal to the abdominal lift pressure, and when the weight was held for periods of up to about 10 seconds and then replaced the pressures remained steady while the weight was held, no breath being taken.

If the weight were held for a longer period, quick, gasping breaths were taken (fig. 3). Each of these respiratory cycles began with an explosive expiration during which the thoracic and abdominal pressures fell rapidly by approximately equal amounts to about half the original lift pressure. Inspiration then followed: the abdominal pressure climbed again to its original lift pressure, while simultaneously the thoracic pressure, whose fall had stopped momentarily, fell again

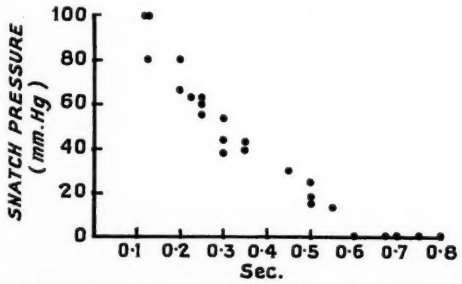

Fig. 4—Snatch pressures in 2 subjects lifting 20 kg. through a vertical distance of 20 cm. at different speeds. Time required was measured in tenths of a second.

rapidly to a subatmospheric level (−5 to −10 mm. Hg). After inspiration had ceased the thoracic pressure rapidly increased again to its lift pressure level. When the weight was replaced on the ground, both pressures returned to their original level after a deep, sighing respiratory cycle.

Of these 32 individual tests, 26 showed an intra-abdominal snatch pressure. In 19 of these 26 there was a snatch pressure in the thorax of a magnitude similar to that in the abdomen.

RAPIDITY OF LIFT

Recordings of abdominal snatch pressures were made during repeated lifts of a 20 kg. weight at different speeds by 2 individuals. These showed (fig. 4) that the frequency of occurrence and the magnitude of the intra-abdominal snatch pressure was proportional to the speed of lift. With very rapid lifts, pressures of 100 mm. Hg were recorded. This series of tests was repeated on five different occasions, making 23 tests in all, and similar results were obtained each time.

Discussion

The results show that there is but little pressure change within either trunk cavity when weights are lifted in the erect posture. They show that there is a considerable increase in pressure when stooping, and that there is a direct relationship between the magnitude of the weight and the height of the pressure induced.

Davis (1956, 1959) and Bartelink (1957) have suggested that such compression of the abdominal contents by the muscles of the abdominal wall caused extension of the trunk by a pneumatic separation of the chest and pelvis. The flexing force exerted by a given weight upon the trunk increases from the upright to the "prone" position, and the finding that there is a parallel increase in pressure in the trunk strongly suggests that this hypothesis is in fact correct.

The intra-abdominal pressures are largest in the stooping and prone positions, so that herniæ and prolapses seem less likely to occur if these positions are avoided when lifting: additionally, of course, bending down to lift a weight is clearly contraindicated in the postoperative management of reparative procedures.

During short lifts the lift pressures were of equal magnitude in both chest and abdomen; this finding may well account for the smallness in the number of patients who attribute their diaphragmatic herniæ to weight-lifting. The fairly frequent occurrence, however, of an abdominal snatch pressure without a similar increase in thoracic pressure shows that weight-lifting can cause quite large pressure gradients across the diaphragm. To maintain a rise in intrathoracic pressure of the magnitudes encountered, the glottis must be closed, and the sudden opening of the glottis when a breath has to be taken may cause the explosive decompression of both cavities (and the grunt) during expiration. During the subsequent inspiration the descending diaphragm rapidly builds up intra-abdominal pressure while lowering that in the thorax and thus again creates a large pressure difference in the two cavities. The high thoracic pressure is re-established by closing the glottis and relaxing the diaphragm. The findings suggest that weight-lifting should be avoided in the postoperative period following repair of diaphragmatic lesions, as with other procedures. The apparent rarity of diaphragmatic herniæ during weight-lifting suggests that factors other than pressure changes are more important in their immediate causation.

Summary

Intra-abdominal and intrathoracic pressures were measured in 5 men while they lifted weights in different positions. In the erect posture, there was no constant increase in intra-abdominal pressure. In the stooping position there was sometimes a large initial increase in pressure in both cavities; this *snatch* pressure was not always observed in the thorax when it occurred in the abdomen. Its occurrence in the abdomen depended on the speed of lift. Following the snatch pressure, there was a constant rise of pressure in both cavities while holding the weight against gravity and holding the breath. The magnitude of this *lift* pressure depended on the position of the trunk and the magnitude of the weight.

The pressure changes due to respiration during lifts consisted of an explosive decompression of both cavities, followed by a rapid increase in the abdominal pressure, while the intrathoracic pressure became subatmospheric and inspiration occurred. When inspiration stopped, the thoracic pressure rose again to the original level of the lift pressure.

The significance of the findings in relation to anterior abdominal wall herniæ, pelvic visceral prolapse, and diaphragmatic herniation is discussed.

My thanks are due to Prof. R. E. M. Bowden for her encouragement and stimulating criticism, to my anonymous subjects for their courage and assistance, and Mr. G. E. Champion and Mr. L. V. Grayson of this department for their ever-ready technical assistance and advice. Part of this work is included in a thesis accepted by London University.

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TREATMENT OF ATYPICAL CASES OF SURGICAL HYPOPARATHYROIDISM

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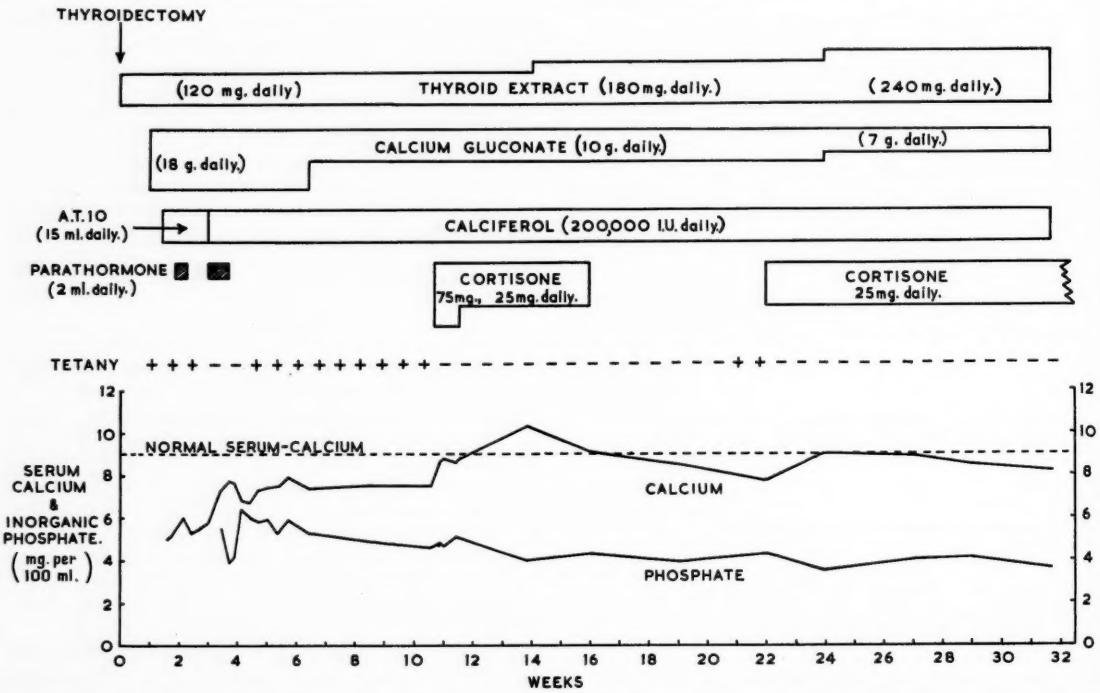
POSTOPERATIVE tetany is usually controlled satisfactorily by oral administration of calcium and calciferol or dihydrotachysterol (A.T.10). Occasionally, however, the patient fails to respond to this treatment. Howard and Connor (1954) suggested that resistance to vitamin-D therapy might be due to a malabsorption syndrome, and the response was favourable when they gave 50 mg. of cortisone daily by mouth in addition to the existing regimen of calcium and vitamin D. We record here a



further case of this type and discuss the mode of action of cortisone.

Hypocalcæmic hypercalciuria is often observed during the treatment of hypoparathyroid patients with calciferol or A.T.10 (Leifer and Hollander 1953, Howard and Connor 1954, Litvak et al. 1958), but only one reference has been found to its occurrence in untreated patients (Albright and Reifenstein 1948). In the following case of surgical hypoparathyroidism hypocalcæmic hypercalciuria was observed both before and during treatment with calciferol. This patient had recurrent renal stones and impaired renal function which necessitated careful control of therapy in order to avoid an excessive urinary excretion of calcium.

Case-records

Case 1.—A woman, aged 48, was admitted on Dec. 13, 1957, with a large non-toxic goitre causing dyspnœa and dysphagia. A subtotal thyroidectomy was performed on Dec. 20, and the patient was given 120 mg. of thyroid extract daily postoperatively. Six days after operation respiratory stridor and signs of tetany developed, and the serum-calcium was 5·0 mg. per 100 ml. She failed to respond to 18 g. of calcium gluconate and 15 ml. of A.T.10 by mouth for eight days and there was no appreciable response when A.T.10 was replaced by 200,000 units of calciferol daily (see figure). A response followed the intramuscular injection of 2 ml. of parathormone daily, but parathormone is not practicable for long-term therapy.

Cortisone (75 mg. daily) was given by mouth for seven days in addition to the existing regimen of calcium and vitamin D, and this resulted in a prompt remission of symptoms, the serum-calcium rising to 8·6 mg. per 100 ml. within twenty-four hours. There were no clinical signs of adrenal insufficiency before this treatment. Fat absorption before and during treatment with cortisone was:

	Intake of fat (g. per day)	*Fat absorbed*
Before cortisone treatment	59·2	91%
During cortisone treatment (75 mg. per day)	59·2	93%

In the subsequent month she received 25 mg. of cortisone, 10 g. of calcium gluconate, and 200,000 units of calciferol daily. During this time she felt well and free from symptoms and her serum-calcium was maintained within normal limits (9·0-10·5 mg. per 100 ml.). Withdrawal of cortisone for six weeks resulted in a fall in the serum-calcium level to 7·7 mg. per 100 ml. and a return of symptoms of hypocalcæmia. On restarting cortisone there was a further remission of symptoms and the serum-calcium rose to 9·0 mg. per 100 ml. For the next three months (May–July, 1958) the patient was maintained on 25 mg. cortisone, 7 g. of calcium gluconate, 200,000 units of calciferol, and 240 mg. of thyroid extract daily. During this period the serum calcium fell slowly from 9·0 to 8·2 mg. per 100 ml., although the patient was free from symptoms of hypocalcæmia during this period.

On July 30, 1958, the patient was readmitted to hospital because of a swelling in the abdomen, and at laparotomy a malignant ovarian tumour and metastases were found.

Case 2.—A woman, aged 48, with bilateral renal calculi, had a right pyelolithotomy in November, 1950, and a left partial nephrectomy for stone in February, 1951. Repeated examination of her blood between 1950 and 1955 showed intermittent hypercalcæmia, the serum-calcium varying between 10·6 and 11·7 mg. per 100 ml. There was also moderate hypercalciuria the daily excretion of calcium varying between 200 and 300 mg. on normal diet and averaging 170 mg. per day on a low-calcium diet (calcium intake 150 mg. per day). There was appreciable impairment of renal function, the urea-clearance being 40% of average normal. No evidence of myeloma, sarcoid, or renal tubular acidosis could be found. Primary hyperparathyroidism was suspected and in May, 1955, her neck was explored, and a number of nodules of tissue were removed. On histological examination these were found to contain parathyroid tissue, but there was no definite evidence of hyperplasia or adenoma.

Postoperatively, the serum-calcium fell to 7·4 mg. per 100 ml. with symptoms of tetany, and 1 g. of calcium lactate and 7 ml. of A.T.10 was given daily by mouth. This resulted in restoration of the serum-calcium to normal (9·0 mg. per 100 ml.), but the urine calcium now exceeded 300 mg. per day (see table). After discharge, she continued to complain of

CALCIUM AND PHOSPHATE VALUES IN SERUM AND URINE (CASE 2).

Date	Medication	Serum		Urine	
		Calcium (mg. per 100 ml.)	Phosphate (mg. per 100 ml.)	Calcium (mg. per 24 hr.)	Phosphate (mg. per 24 hr.)
1955					
May 15	Nil	11·7	3·8	280	740
May 16	Nil	10·8	3·3	260	600
May 17	Parathyroidectomy performed				
May 19	Nil	8·1	4·0	390	160
May 20	Nil	7·6	5·8	425	60
May 21	Nil	7·4	6·5	155	60
June 1	A.T.10 (7 ml.), calcium lactate (1·0 g.) daily	8·8	4·7	358	860
June 2		9·0	5·0	310	460
1956					
Dec. 12	Calciferol (100,000 units)	8·1	4·2	370	833
Dec. 21	Calcium lactate (4 g.) daily	8·4	4·4	348	731
1957					
Feb. 1		7·8	4·7	215	760
Feb. 5	Calcium lactate (7·8 g.) daily	8·2	4·7	270	782
1958					
April 29		8·0	5·2	139	325
April 30		7·8	5·7	160	443
May 3	Calcium lactate (7·8 g.)	7·5	5·3	141	399
May 5	Cortisone (75 mg.) daily	7·6	..	129	316
May 7		7·5	6·2	134	202
June 17	Calcium lactate (7·8 g.) Calciferol (10,000 units) daily	9·0	4·1	244	435

cramp and tingling in her hands and further calcium and calciferol were given orally. Again the serum-calcium level rose and symptoms abated, but again there was an accompanying hypercalciuria. In an attempt to raise the serum-calcium level without causing hypercalciuria, calciferol was stopped and the intake of calcium lactate was increased to 7·8 g. daily. After twelve days on this regime the patient still complained of cramp and tingling, her serum-calcium being 8·3 mg. per 100 ml. and urine calcium 286 mg. per twenty-four hours. She remained on this regimen for the next twelve months during which time she continued to complain of cramp in the legs and tingling in the hands. At the end of this period the serum-calcium was 7·9 mg. per 100 ml. and urine calcium 150 mg. per day.

Oral cortisone (75 mg. daily for six days) had no significant effect on either the blood or urine calcium levels. In an attempt to reduce the daily intake of calcium lactate tablets, 10,000 units of calciferol were given daily and the intake of calcium lactate was halved. This change was followed by severe tetany next day, necessitating intravenous calcium, and the intake of calcium was therefore restored to its original level.

Since May, 1958, the patient has been maintained on gr. 120 of calcium lactate and 10,000 units of calciferol daily. On this regimen she feels well and free from symptoms. Her serum-calcium is 9·0 mg. per 100 ml. and urine calcium 224 mg. per day. There has been no recurrence of stone since operation.

Discussion

In case 1 parathyroidectomy revealed a failure to respond to administered calcium and vitamin D. Cases of this type have been described by Blohm et al. (1953), Howard and Connor (1954), and Dent et al. (1955). Insensitivity to vitamin D may be apparent immediately after operation, as in case 1, or it may develop after a period of satisfactory response to calcium and vitamin D therapy (Blohm et al. 1953, Dent et al. 1955). Dent et al. reported 4 cases of postoperative tetany in which an insensitivity to calciferol developed but responded well when calciferol was replaced by A.T.10. The patients described by Blohm et al. (1953) and ourselves were, however, insensitive to both compounds.

The reason for the failure to respond to calcium and vitamin D is not clear. Blohm et al. observed alleviation of tetany in their patient during two pregnancies and suggested that this was due to the creation of a new source of parathyroid hormone in the fœtus. This view was questioned by Howard and Connor (1954) who suggested that the clinical improvement was due to the increased production of adrenal steroids in pregnancy. They drew attention to the similarity between their patient and the patient with idiopathic steatorrhœa in regard to the response to cortisone; and they suggested that cortisone was beneficial because it promoted the absorption of vitamin D, but no fat absorption studies were carried out. Blohm et al. (1953) could find no evidence of abnormal fat in the fæces of their patient, and no evidence of impaired fat absorption could be found in our case 1. The rapidity of the clinical response to cortisone and of the rise in serum-calcium in our patient and in patients with steatorrhœa (Mackay and Volwiler 1955) suggests that the effect of cortisone is not mediated entirely through vitamin D.

In our 2 cases the effects of cortisone and vitamin D seem to be synergistic, but there is now much evidence to show that these two compounds can also act antagonistically on the serum-calcium level. For example, cortisone lowers the serum-calcium level in hypervitaminosis D (Connor et al. 1956, Verner et al. 1958) and in sarcoidosis with hypercalcæmia (Anderson et al. 1954, Henneman et al. 1956). Further evidence of a cortisone vitamin-D antagonism is seen in the report of Moehlig and Steinbach (1954) that patients with hypoparathyroidism who were well regulated on tachysterol developed tetany when given cortisone for arthritis. It seems that cortisone can affect the serum-calcium level in different ways depending on the sensitivity of the individual to vitamin D.

In case 2 hypocalcæmic hypercalciuria was associated with recurrent renal stone and impaired renal function—a difficult problem in management—and various possible ways of relieving the tetany without increasing urine calcium were considered.

Thyroid hormone may be of value in raising the serum-calcium level in hypoparathyroidism, but it also causes an increase in urine calcium (Aub et al. 1929) and it was therefore considered to be unsuitable for use in the present case. Magnesium deficiency can be a contributory factor in tetany (Miller 1944, Suter and Klingman 1955), but there was no evidence of hypomagnesemia in the present case, the serum-magnesium being 1·9 mg. per 100 ml. (normal 1·7–2·4).

The most satisfactory treatment in this case seems to be large amounts of calcium with a small supplement of vitamin D. The upper limit of normal urine calcium for women is approximately 250 mg. per day (Hodgkinson and Pyrah 1958) and the patient's urine calcium is therefore just within normal limits at present, but continued observation will be necessary.

No definite evidence of hyperparathyroidism could be found on histological examination of the parathyroid tissue removed from this patient and we have concluded that the patient was, in fact, suffering from idiopathic hypercalciuria. In this condition, first described by Albright et al. (1946), the serum-calcium level is usually normal, but there is an excessive urinary excretion of calcium even on a low-calcium diet. Albright et al. considered a number of possible causes and concluded that there is a diminished renal tubular reabsorption of calcium following a *Staphylococcus albus* pyelonephritis (Albright et al. 1953a and b). Jesserer (1957) also concluded that there is a defective tubular reabsorption of calcium in this condition but could find little evidence of staphylococcal pyelonephritis in his series. Our patient's hypocalcæmic hypercalciuria, not attributable to vitamin-D therapy, is taken as further evidence in favour of the existence of a renal tubular defect in idiopathic hypercalciuria. There was no evidence of staphylococcal pyelonephritis in our patient.

Summary

Of 2 unusual cases of surgical hypoparathyroidism, one was found to be resistant to treatment with calcium, calciferol, and dihydrotachysterol, but tetany was relieved when cortisone was given in addition to the existing regimen of calcium and vitamin D. The other responded to calcium and vitamin D but hypocalcæmic hypercalciuria appeared both before and during treatment with vitamin D. It is important in these circumstances to avoid excessive urinary excretion of calcium.

We wish to thank Mr. G. Armitage for permission to treat case 2 and to publish the case-report; Mr. P. M. Zarembski for technical assistance and help with translations; and the staff of the metabolic ward for help with diets and collection of samples.

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Preliminary Communications

THE NEONATAL PULMONARY HYALINE MEMBRANE

AT present there seems to be no generally accepted explanation of the mode of origin of neonatal pulmonary hyaline membranes. A recent editorial in this journal [1] said that it does not yet seem possible to decide whether aspiration of the amniotic-sac contents or damage to the pulmonary capillaries is the responsible factor. From a detailed microscopic study of the lungs of 133 cases of hyaline-membrane disease I have come to the conclusion that neither of these factors is the main cause and that membranes result from necrosis and hyalinisation of epithelial cells lining respiratory bronchioles.

In more than two-thirds (69%) of the cases, remnants of nuclei are found in some of the membranes. In some cases the nuclei are darkly stained and occur in regular order around the lumen of the respiratory bronchiole in a manner corresponding to the normal arrangement of the lining epithelial cells. With advancing nuclear degeneration the cytoplasm swells and shows increasing eosinophilia. In such cases respiratory bronchioles can be found in which the nuclei of a few adjacent cells have disappeared and their cytoplasm forms a continuous mass which is a segment of hyaline membrane flanked on either side by degenerate but still easily recognisable epithelial cells. In the early phases of the disease all gradations can be found—from membranes crowded with nuclei showing only early degenerative changes to those composed entirely of eosinophilic material.

1. *Lancet*, 1958, ii, 945.

The present studies indicate that hyaline membranes occur in respiratory bronchioles, and not in alveolar ducts or in alveoli as commonly stated, and form in situ after necrosis of the lining epithelial cells. The changes include swelling of the cells, degeneration and disappearance of the nuclei, and a change from a colourless to an eosinophilic cytoplasm. That the membranes are composed mainly of degenerate epithelial cellular material is in accord with the failure of several workers to demonstrate particular substances as being components of the membranes. However, the presence of some fibrin [2] and material stained by the Lepehne-Pickworth technique [3] can be readily explained as a consequence of epithelial degeneration in respiratory bronchioles.

Attempts have been made to study the possible contribution of aspirated material to a variety of pulmonary lesions in the newborn by examining smears from the pharynx taken shortly after birth. So far, smears from some 200 cases have been prepared and stained by the Papanicolaou method. In just less than half of the smears numerous ciliated columnar cells are found and in 20% of cases these occur in the form of large masses. The possibility of a relation between the presence of these cells in the pharynx and the cellular degeneration of hyaline-membrane disease has been considered. However, in nearly all the cases the babies showed no signs of respiratory disease in hospital and were discharged well. So far, the most likely explanation for the presence of the ciliated cells in masses is that they are due to dislodgement of mucosal cells from the nose during clearing of the upper respiratory passages after birth. Recent claims [4] using a similar technique for the diagnosis of hyaline-membrane disease during life seem open to doubt.

This concept of an epithelial origin of hyaline-membrane disease implies either an inherent defect in the epithelial cells of respiratory bronchioles exposed to the extrauterine environment or else the action of some injurious agent on the cells in predisposed cases. It appears likely that epithelial immaturity, per se, is the most important single factor; but so far no definite conclusions can be drawn. In the commonly affected group of babies (birthweight 1000–1500 g.) there is also considerable doubt as to the functional activity of the alveolar units. These parts of the lungs appear to be not so much collapsed as incompletely developed. It seems reasonable to suggest, therefore, that in such babies respiratory exchange is largely a function of the respiratory bronchioles, and that degeneration of the lining cells as seen in so-called hyaline-membrane disease is a major factor in preventing this exchange.

The above views on the pathogenesis of hyaline-membrane disease have been expressed in a somewhat similar way only once in the recent literature, by Tregillus [5]; and in subsequent publications he has been given very little credit for his work. For example, last year's editorial in this journal does not mention the paper at all (though it is among the references of a more recent leading article [6]) and the most comprehensive review [7] of hyaline-membrane disease records the concept of an epithelial origin in a few lines but pays no further attention to it. My own investigation was begun without detailed knowledge of these ideas, and it was

2. Gitlin, D., Craig, J. M. *Pediatrics*, 1956, **17**, 64.
3. Lynch, M. J. G., Mellor, L. D. *J. Pediat.* 1955, **47**, 275.
4. Osterlund, K., Hjelt, L. *Ann. Pædiat. fenniæ*, 1959, **5**, 33.
5. Tregillus, J. *J. Obstet. Gynæc. Brit. Emp.* 1951, **58**, 406.
6. *Lancet*, 1959, i, 1234.
7. Tran-Dinh-De, Anderson, G. W. *Obstet. Surv., Baltim.* 1953, **8**, 1.

only when the present concept had resulted from microscopic studies that a careful check through the literature revealed common ground with Tregillus.

It has become quite clear, I believe, that the primary site of hyaline membrane formation is the respiratory bronchiole. In many cases an occasional terminal bronchiole may show similar changes, but alveolar ducts and alveoli are not involved in membrane formation.

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EARLY EFFECTS OF X-IRRADIATION ON SPECIFIC RENAL FUNCTIONS IN DOGS

IRRADIATION is a grave, insufficiently recognised, usually avoidable cause of renal failure [1 2] and hypertension.[3] Clinically, these sequelæ are delayed, so that "acute radiation nephritis" is considered [4] as supervening 6–12 months after radiotherapy. This delay may explain why descriptions of the early structural and specific functional effects of irradiation are not available. The present brief report describes these, as observed after X-irradiation of subcutaneously explanted kindeys of three uninephrectomised dogs.

SERIAL DETERMINATIONS OF SPECIFIC RENAL FUNCTIONS

Dog	Days*	$C_{P.A.H.}$† (ml. per min.)	C_{Cr}† (ml. per min.)	$Tm_{P.A.H.}$† (mg. per min.)	Tm_G† (mg. per min.)
A	−10	118·6	28·2	8·5	88·6
	+ 3	46·6	34·7	—	161·0
	+11	79·5	29·5	3·4	90·9
	+30	24·7	12·1	2·4	39·7
B	−20	107·0	34·9	6·2	109·0
	+ 3	112·5	56·3	3·9	150·0
	+10	104·5	46·8	2·7	106·4
	+21	148·9	50·6	4·2	85·9
C	−12	104·6	53·2	4·8	—
	− 5	104·9	44·1	4·5	—
	+ 3	92·0	40·9	3·3	—
	+10	96·4	37·8	2·9	—
	+23	80·7	32·7	—	—

* Days before (−) and after (+) courses of irradiation.
† Averages of three 15-minute periods of urine collection and measurement of functions.

PROCEDURE

Functions measured were plasma clearance of *p*-aminohippurate (P.A.H.) at low plasma concentrations ($C_{P.A.H.}$) and at concentrations appropriate for measurement of maximum tubular excretory capacity ($Tm_{P.A.H.}$), and glomerular filtration-rate from plasma clearance of exogenous creatinine (C_{Cr}). In addition to these, maximum tubular reabsorptive capacity for glucose (Tm_G) was determined in two dogs, following estimations of $Tm_{P.A.H.}$ and after intervals of several minutes to allow for excretion of excess P.A.H. The function tests were done by standard procedures [5] under light sodium-pentobarbitone anæsthesia.

RESULTS

Irradiation of Entire Kidney

Dogs A and B received a total of respectively 1800 and 3600r by fractional irradiation at rates of 600r every other day from a conventional 200 kV high-voltage röntgen machine. Pre-irradiation renal function tests were done 2 weeks after uninephrectomy and explantation.

Results are summarised in the table. They demonstrate impairment of $C_{P.A.H.}$ and, in the last test, of C_{Cr} in dog A, and persistent impairment of $Tm_{P.A.H.}$ in both dogs. Initial increments in Tm_G subsided and were followed by impairment.

At necropsy, the kidneys of dog A (31 days after irradiation) and of dog B (37 days after irradiation) showed severe hydropic tubular changes. Linear thickening of glomerular membranes and focal pyelonephritis were noted in dog A, acute glomerulitis and extensive interstitial round-cell infiltration in dog B (fig. 1).

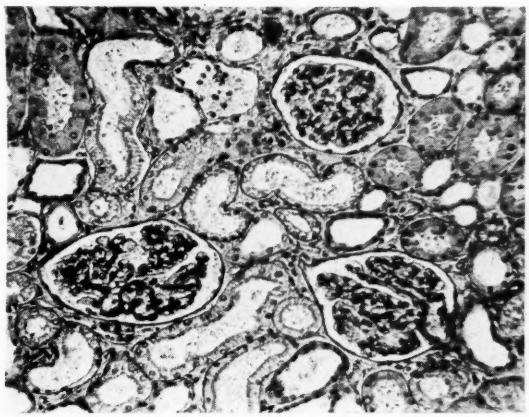

Fig. 1—Necropsy specimen (dog A). Photomicrograph showing focal and linear thickening of glomerular membranes, tubular vacuolisation, and hydropic changes. (Periodic-acid/Schiff × 180).

Irradiation of One-third of Kidney

Two control tests of function were done in dog C, respectively at 2 and 3 weeks after nephrectomy and 1 week after explantation. Explantation did not impair measured functions. Irradiation was limited by a moulded lead screen to the upper pole; this received a total of 1150r delivered in three equal doses at intervals of 2 days each.

Irradiation moderately impaired $C_{P.A.H.}$ and C_{Cr}, more severely depressing $Tm_{P.A.H.}$ (table).

At necropsy, 25 days after irradiation, the irradiated portion was grossly contracted and pale, with indefinite demarcation from the normal tissue (fig. 2). Microscopically, in the irradiated area, the tubules showed varying degrees of hydropic changes, the glomeruli slight membranous glomerulopathy, and the juxtaglomerular apparatus proliferation (fig. 3).

COMMENT

These experiments show that, in the dog, doses of irradiation such as are used clinically in treatment of Wilms's tumour, para-aortic tumour metastases, and gastric ulcer may have significant initial, and also well-

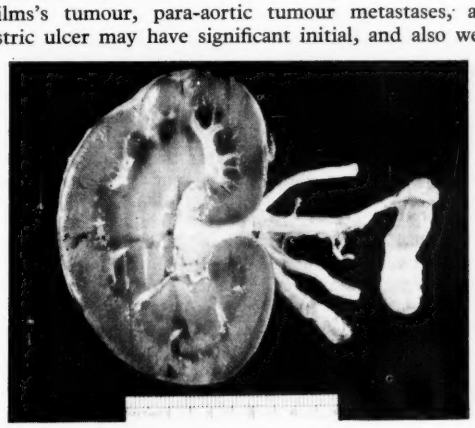

Fig. 2—Necropsy specimen (dog C). Cut surface showing irregularly contracted upper pole. No definite line of demarcation.

1. Luxton, R. W. *Quart. J. Med.* 1953, **22**, 215.
2. Zuelzer, W. W., Palmer, H. D., Newton, W. A., Jr. *Amer. J. Path*, 1950, **26**, 1019.
3. Wilson, C., Ledingham, J. M., Cohen, M. *Lancet*, 1958, i, 9.
4. de Wardener, H. E. The Kidney: an Outline of Normal and Abnormal Structure and Function. Boston, 1958.
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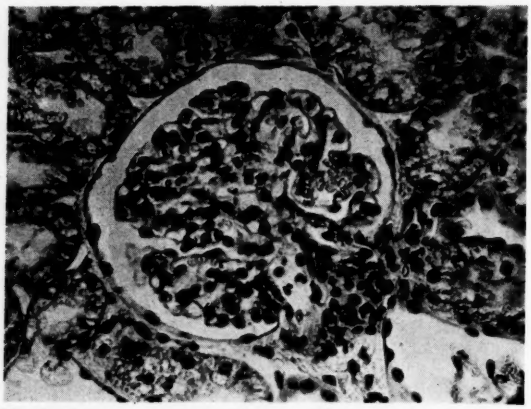

Fig. 3—Necropsy specimen (dog C). Photomicrograph showing proliferation of juxtaglomerular apparatus, slight membranous glomerulopathy, and advanced tubular vacuolisation. (Hæmatoxylin-eosin. ×340.)

recognised delayed injurious effects on renal function and structure. The initial injury is characterised by depression of tubular excretion of P.A.H.; plasma clearances of P.A.H. and creatinine may be only slightly depressed. Increments in glucose reabsorptive capacity were observed at 3 days after the end of irradiation in two dogs; these later subsided. The disparate changes in tubular transports of P.A.H. and glucose, the glomerulopathy noted at necropsy in all three dogs, and the juxtaglomerular proliferation observed in one indicate the desirability of further evaluation of the early renal effects of irradiation. The data indicate that special procedures, such as measurement of $Tm_{P.A.H.}$ may be required to demonstrate the initial phases of renal irradiation injury.

We wish to thank Dr. F. W. O'Brien, of the department of radiology, and Dr. L. J. McCormack, of the department of pathology, the Cleveland Clinic Foundation, for their interest and assistance in this study.

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Medical Societies

HEBERDEN SOCIETY
BRITISH ASSOCIATION OF PHYSICAL MEDICINE

To mark the centenary of the Devonshire Royal Hospital, Buxton, a joint meeting of the Heberden Society and the British Association of Physical Medicine was held at Buxton on July 25 and 26. It was attended also by members of the Canadian Rheumatism Association, the Canadian Association of Physical Medicine, the Nederlandse Vereniging van Reumatologen, and the Manchester Regional Orthopædic Association.

Prednisolone and Analgesics

Prof. J. H. KELLGREN (Manchester) reported the two-year results of a Medical Research Council/Nuffield Foundation trial of the value of prednisolone compared with analgesics in the treatment of early rheumatoid arthritis. Whereas a previous trial had shown no advantage in cortisone compared with aspirin, prednisolone proved superior to other (non-steroid) analgesics in a number of ways. Thus after two years, the patients receiving prednisolone had shown less active disease, were less disabled, and had less joint pain and swelling. Of great interest was the fact that the prednisolone group showed less radiological evidence of joint destruction. Against this was the finding that the prednisolone group developed higher titres for the circulating rheumatoid factor as judged by sensitised sheep-cell agglutination tests. Professor Kellgren was unhappy about this last result; high titres of rheumatoid factor often meant a poor prognosis. Two years was probably not long enough to evaluate the long-term benefits and dangers of this drug, and he did not feel the time was yet ripe to encourage its widespread use in all cases of rheumatoid arthritis. The trial itself had shown that the maintenance dose of prednisolone must be kept low, probably at 10 mg. per day or less. Of eight patients receiving doses of 20 mg. per day or more, for three months or more, five developed major toxic effects such as peptic ulcer or psychosis.

Dr. NEIL CARDOE (London) had completed a placebo-controlled double-blind study of the phenylbutazone derivative γ-hydroxyphenylbutazone (G 27202) in thirty patients with rheumatoid arthritis, and had shown that this drug benefited this disease, both subjectively and objectively. Morning stiffness was signally relieved, and there were fewer complications than in the control group. He felt, however, that though it was a safe and effective analgesic, it had yet to be proved superior to aspirin as an antirheumatic agent.

Dr. R. K. W. KUIPERS (The Hague), in another double-blind trial, had shown the value of compound tablets containing 50 mg. of phenylbutazone with 1·25 mg. of prednisolone in the treatment of rheumatoid arthritis. He had assessed results both by subjective tests of joint function and by objective tests of rheumatic activity, including the measurement of urinary polysaccharide output. Dr. M. F. MCMAHON (Cork) had tried these tablets in 120 patients with arthritis and felt that they were the " best remedy we had yet ". However, Prof. E. L. G. BYWATERS (Taplow) disliked compound tablets because they implied an unvarying ratio of dosage, which might not accord with the varying needs of patients. He did not accept urinary polysaccharides as a valid objective index of rheumatic activity; in one of his patients, salicylate therapy actually increased urinary polysaccharide output.

Circulating Antibody in Rheumatoid Arthritis

Dr. RAYMOND GREENWOOD (London) described results obtained by immunising 22 patients with tetanus toxoid and comparing the antitoxin titres with those of similarily immunised control subjects. The antitoxin response of the group with rheumatoid arthritis was significantly higher than that of the controls, and, though it bore no relation to the differential agglutination titre, was generally greater in those with active disease. These results, he thought, suggested that rheumatoid arthritis was associated with a generally increased activity of the antibody-producing mechanism—a state which would account for the presence of other serological abnormalities, such as increased streptococcal agglutinins, without their being of specific ætiological significance.

Peripheral Nerve Lesions

Dr. PHILIPPE BAUWENS (London) referred to the three conditions generally thought to result from peripheral nerve injury —neurapraxia, axonotmesis, and neurotmesis. Studies of

nerve compression syndromes suggested that two further conditions might occur, both resulting from a progressive obliterating process involving the nerve with a gradual reduction of the cross-section of the axoplasm: local reduction in calibre at the site of the compression might be called " axonestenosis ", and if there was, as seemed likely, some reduction in calibre of the entire fibre distal to the compression this might be termed " anonocachexia ". A reduction in nerve calibre would result in a rise in the threshold of excitability and a decrease in the velocity of conduction, and this would be detected by electromyography, if the affected nerve were stimulated above, and if possible below, the lesion. The site as well as the nature of a peripheral nerve lesion might be determined by examining the myogram. Dr. Bauwens showed a film illustrating the effect of the various lesions he had described on nerve conduction.

Neuronal Innervation of Muscle

Dr. E. N. COOMES (London) discussed the results obtained from studying 5 cases of chronic lower-motor-neurone degeneration by correlated muscle biopsy and electrical reactions, in an attempt to explain the paradoxical finding of normal electrical reactions in weak and wasted muscles. He concluded that this was due to sprouting of unaffected ultraterminal axons, which branched to supply denervated muscle fibres lying in close proximity. Though this sprouting was seen in all lower-motor-neurone lesions, it was only in slowly progressive cases that this " mopping-up operation " masked the signs of denervation.

Immobilising Efficiency of Cervical Braces

Dr. C. M. GODFREY (Toronto) discussed the efficiency of different cervical braces and collars in immobilising the cervical spine by preventing flexion and extension. Radiographs were taken in flexion and extension, before and after the patient put on the brace, and these radiographs were superimposed and measurements made from them. Dr. Godfrey concluded that a felt collar was effective only if it was high at the back, and even then it was less effective than a plastic or metal support. A cervical ruff made from Middlesex bandage was more effective than the standard felt or plastic collar.

Plastic Splints

Dr. J. N. SWANSON (Toronto) reported a new technique of splint making, involving the use of a new plastic (' Durafoam ') allowed to polymerise and harden *in situ*. It was useful both in supportive splints and as a basis for functional splints and self-help devices. The material was extremely strong, light, and washable. It could be remoulded by moderate heat, which was useful in the progressive straightening of flexion contractures. The cost of splints, if one took into account the absence of overheads and greater durability, was no greater than that of plaster-based splints.

New Inventions

A SIMPLE CARDIAC DEFIBRILLATOR

WITH the increased frequency of successful resuscitation following sudden cardiac arrest no operating-theatre, or other department where general anæsthesia is used, should be without some means of achieving electrical defibrillation. Unfortunately the machines available for routine use are heavy and relatively expensive because of the transformer they contain. Hence most hospitals purchase only one or two instead of one for every department.

Essentially, an electrical defibrillator must provide a means of delivering to the heart an electrical shock of 1 amp. for a fifth of a second, at a voltage of 150–200 A.C. The following defibrillator has been devised for emergency use, and can be produced very simply and cheaply (fig. 1). It is not intended to replace the standard model.

The defibrillator has a baseboard 6 in. square, on which is mounted a double pole, press-button switch, and two 1 amp.

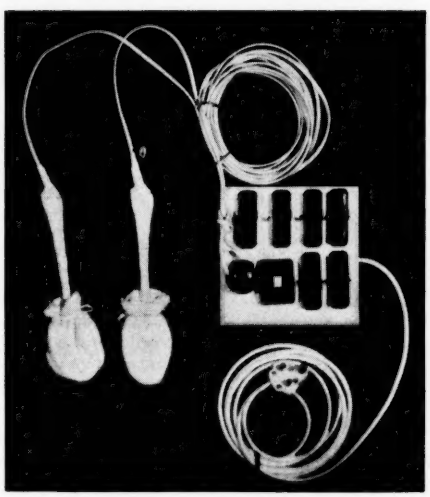

Fig. 1—The defibrillator and electrodes.

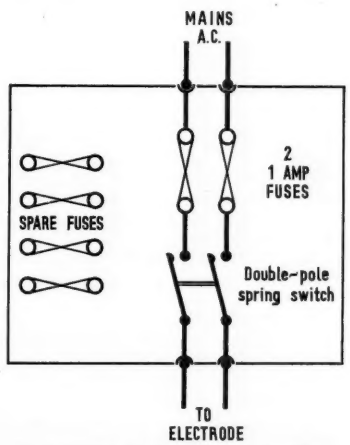

Fig. 2—Wiring diagram of defibrillator.

cartridge fuses. The electrical connections are such that, when the switch is depressed, the patient receives the mains voltage until the fuses blow; this takes a fifth of a second. Four spare 1 amp. fuses are mounted also on the baseboard (fig. 2). The electrodes are constructed from metal tablespoons; the bowls are lightly padded and covered with lint impregnated with sodium chloride, and the handles are insulated with plastic strapping.

The following instructions are affixed to the back of the baseboard:

(1) Wait until cardiac massage has produced COARSE fibrillation.
(2) Wet electrodes, and place on either side of the ventricles.
(3) Press button. (This gives 200 V for 0·2 sec.)
(4) Remove both active fuses, and replace with two reserve fuses.
(5) Repeat defibrillation if necessary.

NOTE: If more than 3 shocks are required, the fuses will have to be replaced in the carriers.

The whole device weighs only a few ounces, and is kept sterile in a polyethylene bag in which formalin tablets are placed.

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Reviews of Books

Hernia

Sir HENEAGE OGILVIE, K.B.E., M.CH., F.R.C.S., consulting surgeon, Guy's Hospital. London: Edward Arnold. 1959. Pp. 135. 28*s*.

A SURGEON'S views on a subject to which through the years he has given particular thought are always interesting, the more so when the subject is as important as hernia and the surgeon as emphatic and frank as Sir Heneage Ogilvie. In this book he does not shrink from telling us the variety of methods he has tried for hernia repair and where he has found them wanting. It goes without saying that he argues his case well and in good style. The work is pleasantly presented with line drawings which are both clear and agreeable.

Textbook of Comparative Histology

WARREN ANDREW, PH.D., M.D., Indiana University, School of Medicine. New York and London: Oxford University Press. 1959. Pp. 652. 120*s*.

THIS book will please all who are interested in the biological sciences and will be useful to many specialists. The contents are wisely arranged in systems rather than animal groups, so that, say, respiratory mechanisms may be more easily compared. Cells, tissues, integuments, and the alimentary, glandular, circulatory, respiratory, excretory, reproductive, and nervous systems are all covered and a final section deals with luminous and electric organs. There are a large number of photographs, of which a few are coloured, and many clear line drawings. The book is intended for American college students, and at the end of each chapter, besides a list of useful references, there is a series of " study questions ".

Dr. Andrew is evidently, and rightly, enthusiastic about the comparative approach to biology, and he does not restrict himself to microscopic anatomy. His general account of physiology and adaptation to general and special conditions makes the book far more interesting and intelligible. The British reader may be somewhat antagonised by the jocular headings to chapters and sections, but as a whole the book is written in a straightforward, though not always elegant, style. Indeed the price is more discouraging than the chapter headings.

Cancer of the Skin

J. C. BELISARIO, C.B.E., M.D., D.D.M., lecturer in dermatology, University of Sydney, senior honorary physician for diseases of the skin, Royal Prince Alfred Hospital, Sydney. London: Butterworth. 1959. Pp. 335. 50*s*.

CANCER of the skin and associated precancerous lesions have a very high incidence in Australia, and this concise lucid book has been written by a physician with a great wealth of experience. Dr. Belisario discusses the basic classification, terminology, and histogenesis of rodent and squamous carcinoma, and their ætiology and precursors, before describing diagnostic measures and specific treatment. He quotes widely and has included a useful bibliography. An appendix gives information obtained from recent publications and personal discussions while the main manuscript was in the final stages of publication. The many clinical and microscopical illustrations, including eight colour photographs, are well chosen and excellently reproduced. The book has been written for all those interested in the early diagnosis and more specific treatment of skin cancers and should prove helpful to general physicians, surgeons, and general practitioners, as well as to dermatologists and radiotherapists.

The Child and the Court

W. E. CAVENAGH, B.SC., lecturer in social study, University of Birmingham. London: Gollancz. 1959. Pp. 239. 21*s*.

OPPORTUNITIES to visit Juvenile Courts are rare even for the child psychiatrists who write reports on children who are appearing as defendants. They, and many others interested in the problems of juvenile delinquency, will welcome Mrs. Cavenagh's thoughtful book. She not only gives an account of the Court and its procedure, but examines it as a means of promoting the welfare of the children who appear before it.

In one of the most interesting chapters, she describes the findings of her investigations into the educational level of the children. She shows what a gulf there is between children so dull and so ignorant and the Bench. She also points out, what is often overlooked, that children, when in Court, are extraordinarily suggestible. Thus, it is easy to put into their mouths an answer which not only is untrue but also damages their case. For these and other reasons she concludes that children need the safeguards of the law more and not less than adults. Her arguments for preferring Court procedure to anything more informal are convincing. But she would like to see the Court regarded as a genuine last resort; and she believes that it could be used less frequently if informal help were given earlier through special educational treatment for the subnormal and maladjusted and through boarding-schools, child-guidance services, and trained social workers.

Early Diagnosis

Editor: HENRY MILLER, M.D., F.R.C.P., physician in neurology, Royal Victoria Infirmary, Newcastle upon Tyne. Edinburgh: E. & S. Livingstone. 1959. Pp. 400. 25*s*.

THIS pleasant, discursive, and informative book, in an easy and unassuming way, conveys much of the essence of good doctoring. The first chapter might well be required reading for medical students the world over. It is not in any sense a textbook of medicine, for it is more concerned with principles than details. Reasonably priced and well produced, it is an ideal book for the doctor on his holiday.

Diseases of Metabolism

Detailed Methods of Diagnosis and Treatment. 4th ed. Editor: GARFIELD G. DUNCAN, M.D., professor of medicine, University of Pennsylvania, director of medical divisions, Pennsylvania Hospital and the Benjamin Franklin Clinic. Philadelphia and London: W. B. Saunders. 1959. Pp. 1104. 129*s*. 6*d*.

MUCH has happened in the metabolic world since the last edition of this book appeared in 1952. New subjects, such as the relationship of the dietary fatty acids to atherosclerosis, have appeared on the clinical horizon, and there have been many remarkable developments in some of the old problems —intermediary metabolism, for example. It is still not possible, however, to wave a wand over a gouty toe and watch it subside, and the laws of thermodynamics still preside over the treatment of obesity. Prof. Garfield Duncan and his collaborators have done their best to bring all these matters up to date, and admirers of previous editions will have few disappointments in this one. A little new blood has been infused in the way of new authorship, but the book remains essentially unchanged in balance and form. Each chapter still ends with a formidable list of the original papers cited, and this alone will ensure that the book goes forward as one of the standard works of reference on general metabolic disease.

Handbook of University College Hospital, London (Shrewsbury: Wilding & Son. 1959. Pp. 130. 10*s*. 6*d*.).—Each London teaching hospital has its own handbook for students. Most of these contain a good deal of useful information, but each generation's needs are different, and the text too easily silts up with yesterday's dogma. Sometimes, too, there is a lag before modern ideas are incorporated. Neither of these criticisms can be levelled at the latest edition of U.C.H.'s handbook. The editors, Dr. T. D. Whittet, Dr. M. Maizels, Dr. Joan Stokes, and Dr. F. V. Flynn, are to be congratulated on producing a slim volume which contains a great deal of accurate, up-to-date, and useful information and a minimum of anything else.

Surgical Technique. (2nd ed. London: Heinemann. 1959. Pp. 41. 40*s*.).—Mr. Stephen Power has carefully compiled this vademecum of general surgical know-how for the benefit of house-surgeons and young surgeons. It will set them thinking about their smallest actions.

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THE LANCET

LONDON 22 AUGUST 1959

Father or Uncles?

MUCH of the recent correspondence on the Mental Health Bill has centred on the merits, and particularly the demerits, of the medical superintendent. Whereas this post is now a rarity in the rest of the English hospital service, it has been preserved in mental hospitals by regulations which require that some one person shall be appointed to take legal responsibility for all the patients. Under the new Mental Health Act the Minister of Health may well decide that the "responsible medical officer" shall in future be the consultant in charge of the case, and may abolish the obligation on mental-hospital authorities to appoint a doctor with special administrative powers. The peculiarity of mental hospitals would thus be reduced, and they would be brought more closely into line with the rest of the hospital service—which is in itself desirable. But, though nearly everybody agrees that the autocratic rule which medical superintendents have sometimes exercised is an anachronism, and that other consultants in mental hospitals should have complete clinical responsibility for their patients, the reforms clearly necessary should not be carried so far as to deprive these hospitals of the kind of leadership which has done so much for some of them in the past and which many still so plainly need.

This is part of the larger question whether, or in what circumstances, hospitals gain by having a doctor as executive administrator. Most of the old local-authority hospitals—which between them held more than half the beds in this country—were directly administered by a medical superintendent (and less directly by the medical officer of health). When, under the National Health Service, the hospitals were transferred to regional boards, clinical responsibility passed from the medical superintendent to the consultant in charge of the patient; and, though a few surviving superintendents have combined part-time administration with work in their own wards or departments, the accepted pattern in most English hospitals since the start of the National Health Service has been the one that was usual in the former voluntary hospitals—i.e., the day-to-day details of medical administration are handled by the chairman of the medical staff committee, and/or the senior resident, working with or through the hospital secretary. Unfortunately, though this can be satisfactory in the smaller general hospitals, the growing complexity of administration makes it inadequate for the larger ones. In considering the new situation a few years ago the Bradbeer Committee[1] recognised that "something more is needed"; and, though it did not favour the return of medical superintendents as previously seen in municipal hospitals, it did think that most of the larger general hospitals should have a "medical administrator". He was to be a consultant in active clinical practice, with taste, time, and talent for this kind of administrative work, who would be selected jointly by representatives of the medical staff committee and of the hospital management committee (with a little help from the regional hospital board). He was to be appointed for only four or five years but could be reappointed.

From this plan the mental hospitals were excepted. The Bradbeer Committee had been told that the nature of these hospitals, and that of their patients, demand the constant presence of someone in authority, who must be able to intervene in any matter affecting a patient. Now that we have a new Mental Health Act, is this argument still valid? If the legal reasons are removed, are there still administrative reasons why arrangements at mental hospitals should differ from those at other hospitals? Dr. SHAW and Dr. SAMUEL, whose article we publish on p. 170, seem to think not. They describe how Belmont Hospital, taking advantage of the fact that technically it is not a mental hospital, decided to do without a medical superintendent and appointed instead a consultant as "medical administrator"—very much as was recommended by the Bradbeer Committee, except that, experimentally, he was appointed for only two years. But they also mention that the management committee was a little uneasy about such an appointment because it wondered whether a member of the staff, nominated by his colleagues, would suffer from divided loyalties when asked to obey the hospital committee's directions. Compared to the medical superintendent, a "medical administrator" thus nominated is far less clearly an agent of the hospital authority; and, though the Belmont arrangements have evidently worked well, the administrator's status would require more precise definition before these arrangements could be adopted generally in mental hospitals. "The administrative structure which has been evolved is based on the medical staff committee," Dr. SHAW and Dr. SAMUEL say; and though one may share their feeling that "if the administrator is to have a good working relationship with his colleagues, he must in large measure be their representative" one can also understand the reluctance of the regional board to give this doctrine their sanction. After all, the medical staff already have a representative in the chairman of their committee.

In his letter this week Dr. FISHER recapitulates the main reasons why many people think that a mental hospital still needs a kind of management different from that of a general hospital—why it still needs a medical superintendent with more power and influence and security of tenure than a medical administrator on the Bradbeer-Belmont model. His first and perhaps most telling argument is that a mental hospital (or any hospital where patients stay a long time) is or should be a therapeutic community. To the patient with a mental illness the character and atmosphere of the hospital as a whole may matter far more than any course of treatment; and we now recognise that without a positive effort to make a hospital therapeutic it can very easily be the

1. Central Health Services Council: Report of the Committee on the Internal Administration of Hospitals. 1954.

reverse—exacerbating and prolonging the illnesses it is supposed to be curing. Who is to make this positive and strenuous and continuous effort? Whose job is it to see that the hospital as a whole becomes steadily more therapeutic and less noxious—that it has a consistent policy of improvement and loses no chance of useful innovation? The hospital secretary? Only exceptionally can he be equal to such a task; for the primary function of a secretary or house-governor is to run his hospital efficiently; and, though he may help to bring a backward hospital up to date, he is unlikely to be at the forefront of change—especially the rather clinical kind of administrative revolt now going on in so many hospitals. (In many hospitals, to turn the existing secretaries into secretary-superintendents with much of the medical superintendent's lost authority would certainly ensure the preservation of things as they are.) But can we safely count on the necessary thought and work coming from the medical staff? Even if one of them becomes part-time medical administrator for a few years, as at Belmont, how likely is he to look beyond day-to-day administration? If some medical superintendents have become tyrants, we should not forget that some have become pioneers. And one reason why they turned into pioneers is that they were placed in a highly responsible position in which they identified themselves with the hospital and put their whole heart and soul into it.

TETLOW [2] has shown that in a mental hospital authoritarianism tends to cause the breakdown in personal relations that is so fatal to a therapeutic community; and some of the more emphatic opposition to medical superintendency is evidently born of unhappy recollections. As we have lately noted,[3] study of the mental hospital reveals its structural resemblance, in many ways, to the family—in which the father can cause similar havoc. On the other hand, in the hospital as in the family, a father figure can be no small asset: and all the errors of fathers and superintendents in the past need not necessarily be reproduced by their successors in the more liberal climate of today. People being what they are, the head of an institution inevitably receives transferred emotions from those working with him; and, if he happens to be a person who can use the transference with vision and understanding, it may enable him to do things impossible without it. Looking at the advances now being made, under difficulties, in a dozen mental hospitals in this country, few would say that the race of great superintendents is extinct. Would these doctors have done so much for their hospitals and for medicine if they had been consultants taking a turn as medical administrator? Ought we not to think twice before vengefully abolishing the stable father figure and replacing him by a rota of uncles?

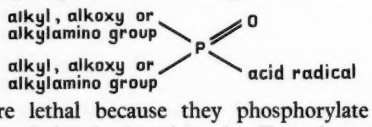
Some decision about this must doubtless soon be made. But we earnestly hope that it will not impose uniformity. Having learnt something by experience, can we not go on to learn even more by experiment? Many mental hospitals—especially those in a static phase—would be well served by medical administrators as at Belmont; but others, surely, should still offer the larger opportunities required by the man with a genius for administration or the man who can see how to do things in some new and better way.

2. Tetlow, C. *Lancet*, 1957, i, 89.
3. See *ibid.* 1959, i, 83.

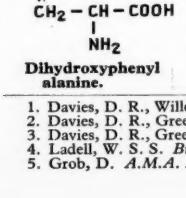
Organophosphate Poisoning

DURING the second world war a new deadly weapon was added to the arsenal of 20th-century warfare—the nerve gases. Though these lethal organophosphates were never brought into military action, they are now widely used as insecticides and have thus become one of the hazards of work on the land. If the recommended precautions are taken, there should be no cases of poisoning from them; but protective clothing, masks, and gloves are tiresome, and familiarity breeds its usual contempt. Every year in this country a few people are poisoned—mostly while spraying fruit trees. In addition, as Dr. TOIVONEN says in the paper from Finland which we publish this week, one of these substances, parathione, is used increasingly as a means of suicide. Hence the progress made in the treatment of organophosphate poisoning needs to be more widely known. Some brilliant work at the Chemical Defence Experimental Establishment, at Porton, near Salisbury, is described by D. R. DAVIES and his collaborators A. L. GREEN and G. L. WILLEY [1–3] and W. S. S. LADELL.[4]

Organophosphates are of the general structure:



They are lethal because they phosphorylate cholinesterase and thereby inactivate it. For a long time the only practical remedy for this was to counteract the accumulation of acetylcholine by administering its antagonist atropine, supported by artificial respiration.[5] But atropine has unpleasant pharmacological effects of its own; and, though it will reverse the muscarinic and some of the central effects of acetylcholine, it does not reduce its nicotinic action. A more rational treatment would protect or restore the activity of cholinesterase rather than accept its inactivation and merely counteract the accumulation of acetylcholine. Protection of cholinesterase might be achieved by a compound which competes with it for the organophosphate, and reactivation by a substance which would dephosphorylate the inhibited enzyme. For both purposes essentially the same type of compound is needed—one which would be highly reactive with the inhibitor in the first case, and with the inhibited enzyme in the second.



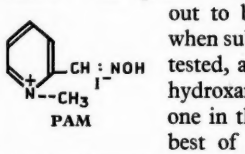
Dihydroxyphenyl alanine.

The rapid reaction of organophosphates with enzymic protein led to investigation of the effects of simple aminoacids; but most of these proved ineffective, and only one of them—dihydroxyphenyl alanine (DOPA)—was found to combine surprisingly quickly with some

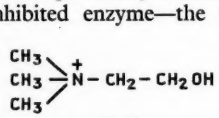
1. Davies, D. R., Willey, G. L. *Brit. J. Pharmacol.* 1958, **13**, 202.
2. Davies, D. R., Green, A. L., Willey, G. L. *ibid.* 1959, **14**, 5.
3. Davies, D. R., Green, A. L. *Brit. J. industr. Med.* 1959, **16**, 128.
4. Ladell, W. S. S. *Brit. med. J.* 1958, ii, 141.
5. Grob, D. *A.M.A. Arch. intern. Med.* 1956, **98**, 221.

of the organophosphates. When its activity was found to be due not to the alanine, but to the *o*-dihydroxyphenyl, a number of *o*-hydroxybenzene derivatives were tested; but, though some of them reacted with organophosphates, no evidence has been published that they are useful as antidotes or that they reactivate inhibited cholinesterase. Another line of approach was the catalytic effect of heavy metal ions on hydrolytic reactions [6]: ammonium molybdate proved to be a potent reactivator of inhibited cholinesterase,[7] and metal ion complexes induced hydrolysis of organophosphates.[8] But, again, none of these have yet been shown to have any value in treatment.

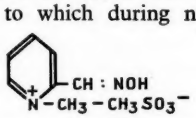
The greatest success has come from the suggestion that, as hydroxylamine (NH_2OH) is highly reactive with carboxylic esters, it might also react with phosphate esters.[9] In point of fact hydroxylamine turned out to be only mildly effective, but, when substituted hydroxylamines were tested, a high reactivity was found in hydroxamic acids,[10] and an even higher one in their analogous oximes.[11] The best of the oximes tested was pyridine-2-aldoxime methiodide, known as PAM.[12 13] In addition to the nucleophilic oxime group this compound carries a quaternary ammonium group, and therefore incorporates also the enzyme-reactivating property of choline. This effect of choline is ascribed to anchorage of the quaternary ammonium to the anionic site of the inhibited enzyme—the site to which during normal



PAM



Choline



P2S

hydrolysis the choline part of acetylcholine becomes attached. PAM and the corresponding soluble methane sulphonate P2S have been amply proved useful in organophosphate poisoning in animals. DAVIES and GREEN,[3] in an instructive table summarising ten publications from Britain, France, Germany, Italy, and the United States, show the effect of PAM (or P2S) plus atropine on mice, rats, guineapigs, rabbits, and dogs poisoned with eleven different organophosphates. Evidently all the compounds which carry alkyl or alkoxy radicals have been successfully counteracted; on the other hand, tabun and OMPA, which contain alkylamino radicals, could not be reversed in their effect, and parathion also presents a problem of its own. Parathion is itself only the precursor of the lethal paraoxon which is formed from it in vivo; and, as this conversion is slow, repeated treatment with PAM is necessary.[14] It was concluded from animal experiments by DAVIES and WILLEY [1] that at least 30 mg. of PAM or P2S per kg. body-weight could safely be given to man by intramuscular injection. LADELL [4] has given P2S in doses over 1 g. intravenously to normal people, and over 5 g. by mouth without ill effect. NAMBA and HIRAKI,[15 16] in Japan, have given PAM intravenously in doses up to 2 g. They treated thirty-nine cases of parathion poisoning, and with 1 g. the signs of poisoning almost disappeared except in five of those most affected. In these five further improvement was obtained with additional PAM, and only one patient, who had taken a very large amount of parathion, died despite 2 g. In the Japanese patients PAM relieved the muscarinic as well as the nicotinic effects of parathion, which is contrary to the experience of GROB and JOHNS,[17] who found no effect on the muscarinic signs in man. Like the Japanese workers, they administered PAM intravenously quite safely in doses up to 2 g.; but the discrepancy between their results and those of NAMBA and HIRAKI on the muscarinic action of parathion has yet to be explained.

In view of the uncertainty whether PAM counteracts in man the muscarinic as well as the nicotinic effects of anticholinesterases it seems advisable to combine PAM or P2S always with atropine, as was suggested by LADELL at a recent meeting of the Faculty of Anæsthetists.[18] NAMBA saw a clearing of consciousness with PAM, and the same thing was noted by Danish workers [19] when they treated a case of suicidal parathion poisoning. This is hard to understand; for, in animals at least, the blood-brain barrier is resistant to penetration by PAM. But clearly one cannot tell solely from observations on animals how man will respond to the various organophosphates or to their antagonists. Even within the same species, genetic differences must be expected to cause differences of response. For *Anopheles gambiæ* DAVIDSON [20] has shown that a single gene is responsible for the resistance to dieldrin shown by some of these mosquitoes, and similar results have lately been recorded for *Lucilia cuprina*.[21] Nothing is known about a genetic variation in level or type of acetylcholinesterase in man, but genetically determined differences in the level of human pseudocholinesterase have been reported by LEHMANN and RYAN [22] and similar differences in response to inhibition by dibucaine by KALOW and STARON.[23]

In our correspondence columns on June 6 Dr. E. F. EDSON gave the names and addresses of six establishments in Britain where supplies of PAM for injection can be obtained for ready use in emergencies; and the medical division of the Chemical Defence Experimental Establishment at Porton runs an emergency service for treatment of organophosphate poisoning. The days are long past when the only hope was that massive doses of atropine would save the patient.

6. Jandorf, B. J., Wagner-Jauregg, T., O'Neill, J. J., Stolberg, M. A. *J. Amer. chem. Soc.* 1952, **74**, 1521. Augustinsson, K. B. *Acta chem. scand.* 1952, **6**, 959. Berry, W. K., Fellowes, K. P., Fraser, P. J., Rutland, J. P., Todrick, A. *Biochem. J.* 1955, **59**, 1.
7. Hobbiger, F. *Brit. J. Pharmacol.* 1956, **11**, 295.
8. Wagner-Jauregg, T., Lies, T. A., Owens, O. O., Proper, R. *J. Amer. chem. Soc.* 1955, **77**, 922. Courtney, R. C., Gustafson, R. L., Westerback, S. J., Hyytainen, H., Chaberek, S. C., Martell, A. E. *ibid.* 1957, **79**, 3030.
9. Jandorf, B. J. *J. Amer. chem. Soc.* 1956, **78**, 3686.
10. Hackley, B. E., Plapinger, R., Stolberg, M. A., Wagner-Jauregg, T. *ibid.* 1955, **77**, 3651.
11. Green, A. L., Saville, B. *J. chem. Soc.* 1956, p. 3887.
12. Davies, D. R., Green, A. L. *Disc. Faraday Soc.* 1955, **20**, 269.
13. Wilson, I. B., Ginsburg, S. *Biochim. biophys. Acta*, 1955, **18**, 168.
14. Wilson, I. B., Sondheimer, F. *Arch. Biochem.* 1957, **69**, 468.
15. Namba, T. *Naika no Ryoiki* (Field of Internal Medicine) 1958, **6**, 84; quoted by Davies and Green (ref. 3).
16. Namba, T., Hiraki, K. *J. Amer. med. Ass.* 1958, **166**, 1834.
17. Grob, D., Johns, R. J. *ibid.* p. 1855.
18. *Lancet.* 1959, i, 980.
19. Karlog, O., Nimb, M., Poulsen, E. *Ugeskr. Laeg.* 1958, **120**, 177; quoted by Davies and Green (ref. 3).
20. Davidson, C. *Bull. Wld Hlth Org.* 1958, **18**, 579.
21. Shanahan, C. J. *Nature, Lond.* 1959, **183**, 1540.
22. Lehmann, H., Ryan, E. *Lancet*, 1956, ii, 124.
23. Kalow, W., Staron, N. *Canad. J. Biochem. Physiol.* 1957, **35**, 1305.

Annotations

MEDICAL ELECTRONICS

THE second International Conference on Medical Electronics took place recently in Paris. The fact that it was held within a year of the first, that it was attended by several hundred people from all over the world, and that over 150 original papers were presented, is evidence of the vigour with which this progeny of Hygieia and Hephæstos is growing. For those who have little understanding of medical electronics, but who are aware that their colleagues who use its techniques wield a powerful magic, the conference, in the variety of the applications it displayed, was an eye-opener, and even for the general practitioner there were developments of interest.

The gastroenterologist can now persuade his patient to swallow a radiosonde no larger than a cherry stone. During its passage through the alimentary tract it will obediently transmit information about the temperature, or the pressure, or the pH, in its immediate environment, and will even draw a sample of intestinal contents at the whim of the operator, and preserve it for subsequent examination. There is promise, too, of further help for the paralysed or limbless. Potentials from appropriate muscles can be picked up, amplified, and made to control a gas-valve. This causes gas under pressure to work an " artificial muscle " which gives movement to a paralysed limb or to a prosthesis replacing one. A " solid image " projection microscope, by causing the objective to scan rapidly through its depth of focus and the screen to move back and forth in unison, can give a three-dimensional presentation of the object. An electromagnetic flowmeter, attached to the aorta of a dog, and left in situ, can record cardiac output and other parameters of the cardiovascular system in the dog as it runs about. Ultrasonics can destroy bacteria, probe body cavities and organs to detect tumours, and will perhaps be able to disintegrate urinary calculi in situ.

The perplexed diagnostician is not forgotten. The signs and symptoms of all the diseases in the textbook can be fed into the memory store of a computer. The signs actually observed in a puzzling case can then be referred to it, and the various possible diagnoses, in order of probability, will be printed out in a matter of seconds, with suggestions for further tests which might be helpful. If it be objected that the machine is doing no more than imitate the mental processes of the medical practitioner, it can be pointed out that the machine needs less training, and is subject to fewer aberrations, than the doctor. Computers can also have a place in an emergency bed service, where one machine can do the work of half a dozen girls with unfailing accuracy and good humour.

There are few branches of medicine which cannot benefit from the engineer's ability to control electron streams; and though it is hard to define the boundaries of medical electronics there is no doubt of its importance.

PSEUDO-FLATULENCE

AMONG the many contributions Sir Arthur Hurst made to a proper understanding of functional disorders of the gastrointestinal tract is one on what he called " pseudo-flatulence ". Although he made passing mention [1] of this distinctly uncommon condition in 1918, it was not until 1933 that he presented the clinical picture in some detail.[2] The patient, more often female than male, and commonly adult or even elderly, complains only of distension of the abdomen, which may be so obvious as to be a considerable distress and embarrassment. The distension may persist for weeks, but more often it recurs in attacks of only a few hours' duration. For these there is no obvious cause, and, all too often, a reluctant diagnosis of intestinal obstruction is the unhappy prelude to a negative laparotomy when the entire stomach and intestine is found, rather surprisingly, to be empty of gas. A lucky patient may escape operation when, during the induction of anæsthesia, the abdominal distension collapses like a pricked balloon, without, however, the expected accompaniment of a free discharge of flatulence, either from above or from below.

Hurst believed the condition to be due to precisely the same causes as the abdominal distension seen in pseudocyesis, on which J. Y. Simpson made such shrewd observations more than a century ago.[3] Although the condition came to be recognised in his own hospital,[4] it received scant attention in the literature [5] until 1949, when Alvarez [6] wrote from the Mayo Clinic on what he chose to call " the hysterical type of non-gaseous abdominal blating ". It has, over the years, been given a variety of names: " hysterical meteorism " [5] " hysterical abdominal proptosis " [7 8] " pseudo-tympanites " [4] and (most colourful of all) " ventre en accordéon ".[9]

Hurst believed the condition was due to a sustained contraction of the diaphragm, which was observed on screening to be low in position and to move only a very little on respiration. He further noticed that the lower ribs were drawn inwards, apparently by the strong pull of the contracted diaphragm. The truth of this assertion was subsequently affirmed by later workers, and has recently been sustained by a more scientific inquiry from Brisbane by Tyrer and his colleagues.[10] Healthy volunteers were able, after a little practice, to produce (but not to sustain for long) varying degrees of abdominal distension by contraction of the diaphragm, which was seen to descend 7 cm. or more (as measured from a radiograph). Intra-abdominal pressure, as recorded in the stomach, rose by 60–70 cm. of water and at the same time there was a slight decrease in the circumference of the lower part of the chest. Although voluntarily exaggerated lordosis (the presence of which has often been noted in the recorded cases) made the abdominal distension more obvious, this manœuvre did not add to the abdominal girth, a fact also noted by Simpson [3] in his comments on spurious pregnancy.

Whether or not the qualifying " hysterical " is in such cases allowable, it seems highly likely that a diligent inquiry will, in most cases, reveal a significant underlying psychological disturbance. It would, however, be wise always to bear in mind that Hurst [1] thought that " pseudo-flatulence occurs most frequently as a complication of some organic disorder, such as gastric ulcer or colitis, or after a blow on the abdomen "—a view that

1. Hurst, A. F. Medical Disease of the War; p. 169. London, 1918.
2. Price, F. W. A Textbook of the Practice of Medicine; p. 568. Oxford, 1933.
3. Simpson, J. Y. The Obstetric Memoirs and Contributions of James Y. Simpson; vol. 1, p. 300. Edinburgh, 1855.
4. Gill, W. G., McArdle, M. J. *Guy's Hosp. Rep.* 1934, **84**, 94.
5. Purves-Stewart, J. The Diagnosis of Nervous Diseases; p. 661. London, 1945.
6. Alvarez, W. C. *Arch. intern. Med.* 1949, **84**, 217.
7. Roussac, N. J. *Gastroenterology*, 1951, **17**, 133.
8. Ewing, M. R., Miller, J. H. D. *Brit. med. J.* 1935, ii, 1124.
9. Kaplan, L. De la pseudotympanite nerveuse; ou ventre en accordéon. Thesis. Paris, no. 30, 1900.
10. Tyrer, J. H., Murphy, K. J., Emmerson, B. T. *Aust. Ann. Med.* 1958, **7**, 292.

has lately been restated [11] (" the danger of over-investigation of these cases is far less than the danger of neglecting to do so . . .").

HOPE OR CONSOLATION?

WE who live in the more prosperous countries, where people grumble if they have to wait an hour to see a doctor, find it hard to imagine that millions in less fortunate lands live and die without ever seeing one, however desperate the need. When we do imagine it, our consciences cannot fail to be stirred, and that of Dr. William Walsh, of Washington, has been stirred to some purpose.[12] He is the head of " Project Hope ", which is to send a hospital ship to South-East Asia. The aim is to give treatment and to train the local populations in elementary nursing and hygiene. The ship is due to sail on January 22 from San Francisco to spend eight months in Indonesia, and it may visit Vietnam and other countries.

The vessel itself is a hospital ship now in the reserve fleet of the U.S. Navy, which will charter it to the project at nominal cost and on October 1 will begin to overhaul and equip it. The conversion is being paid for out of Mutual Security funds; the managerial expenses will be borne by an American shipping company; and the remaining costs will be paid by the project, supported by public subscription. The ship will carry 10–15 permanent doctors, as well as rotating groups of 35 who will be flown to the ship every four months. So far 1000 doctors and nurses have applied. The ship will have 422 beds; besides this there will be a 500-bed mobile hospital for journeys to the interior, and teams of about 6 doctors and 2 nurses will fly to other areas; they will work with local doctors.

Such a floating hospital could do much valuable work. There must be a vast accumulation of patients whose lives could be made happier and more productive by a single surgical operation, and many with chronic medical conditions who could be set on the road by a short period of treatment and instruction. Education in hygiene and child care could also achieve much. Those whose more acute illnesses (from meningitis to cancer) happen to become manifest while the hospital is at hand will also benefit. Moreover, the experience gained will prove useful if the much larger scheme proposed by Commander Frank Manson, U.S.N.[13] for a fleet of six ships to undertake disaster relief, education in agriculture, and many kinds of aid besides medical care—is ever put into practice. One only wonders whether the money to be used in the project (estimated at $3^1/_2$ million dollars in the first year) might not be better spent on some other scheme which might achieve more lasting results for whole communities. But if we cannot say which way of spending the money would do more for human happiness, there is no doubt which will better stir the imagination—both of those who give and of those who receive. It is understandable that a project with so individual a flavour should appeal to so individualistic a people as the Americans—who might be less eager to subscribe to a less dramatic cause, in which case the money would not be provided anyway. We may hope that the personal contact between doctors and patients will help a little to improve the relations between East and West. The real need—for permanently improved medical services—must await a permanently improved economy; and in many places this means vastly greater aid from the richer countries (including our own) than has yet been contemplated.

The Navy wishes the ship to retain her present name, *Consolation*, while the members of the project would like to change it to *Hope*. If the ship is to arrive at a port, do a little good work, and sail away for ever, her old name will be more appropriate: but if she is a harbinger of greatly increased economic and medical aid to the poorer countries, then she may proudly and appropriately be called *Hope*.

CHEMOTHERAPY IN RENAL TUBERCULOSIS

THOUGH the results of chemotherapy in pulmonary tuberculosis have been widely acclaimed, it is perhaps not so well known that the response in urogenital infection is equally striking. Fifteen years ago the standard treatment for renal tuberculosis was still ablative surgery when practicable, supplemented by palliative sanatorium care for bilaterally active or widely disseminated disease. Nephrectomy, which usually involved the removal of at least some functioning renal tissue, was clearly not ideal, and the progressive morbidity in many of the more advanced cases, even under the best possible conditions, was often distressing. The ultimate mortality from renal failure and infection was well over 50%.

Nowadays the picture has completely changed and the full application of modern methods of chemotherapy has made it very rare for any patient with urogenital tuberculosis to die from the disease. This remarkable improvement has come about in stages related to modifications in the chemotherapeutic regime, and it is thus only recently that sufficient statistical evidence has accumulated to permit its full assessment. Among information now available from many centres, the report of Halkier and Meyer [1] from the Finsen Institute at Copenhagen emphasises an experience which is becoming common to those responsible for the collective management of renal tuberculosis. The report compares the course of 90 cases treated purely conservatively (control group 1943–49) with a subsequent series of 222 patients (1949–59) who received chemotherapy. The latter are divided into two groups, the earlier of which (132 cases, 1949–54) received various combinations of streptomycin (or dihydrostreptomycin) with *p*-aminosalicylic acid (P.A.S.) and later isoniazid over different periods. The experience thus gained led to a standard six-month course of sustained triple-drug therapy which was applied to the remaining 90 patients during 1955–59.

From an analysis of the three groups it can be concluded that the experimental period of chemotherapy is now finished in all essentials. Renal tuberculosis responds so well to a properly organised regime that chemotherapy is now indicated whenever there is renal tissue to preserve. Using sustained simultaneous treatment with dihydrostreptomycin, P.A.S., and isoniazid over an initial period of six months Halkier and Meyer were able to secure a stable urinary conversion rate approaching 90%. They conclude that this combination practically eliminates the risk of drug resistance so that any further treatment that is necessary will be effective. Resection of the kidney is seldom required except when drug-resistant recurrence can be attributed to a definite localised focus. To ensure these advantages of a well-planned course of treatment, haphazard or half-hearted chemotherapy should be sternly discouraged.

Dr. C. P. RHOADS, director of the Sloan-Kettering Institute for Cancer Research, New York, died on Aug. 13 at the age of 61.

11. Goldie, L. *Brit. med. J.* 1955, ii, 1565.
12. *New York Times*, July 13.
13. *Life*, July 27, p. 17.

1. Halkier, E., Meyer, J. *Danish med. Bull.* 1959, **6**, 97.

Special Articles

MEDICAL ADMINISTRATION IN PSYCHIATRIC HOSPITALS

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THE Mental Health Bill has once again focused attention on the vexed question of medical administration in mental hospitals. Vigorous attack has been made on the hierarchical mental-hospital administrative structure, and the medical superintendent himself has come in for particularly severe criticism. At a time when policies are being formulated, it may be of interest to describe in some detail a successful experiment in medical administration at Belmont Hospital.

Medical Superintendents—For and Against

It is probably true to say that medical administration in mental hospitals is a special aspect of the larger problem of that in hospitals generally. Before the National Health Service, autocratic medical superintendents of teaching hospitals were not unknown, and in the old poor-law hospitals the medical superintendent had virtually the power of life and death over the patients, as Somerville Hastings has observed.[1] In mental hospitals the medical superintendent was the paramount officer in law. The Lunacy Acts required the visiting committee to appoint a medical superintendent, and the Board of Control insisted that he had power to suspend any member of the staff. In fact, he was the only hospital medical officer with a legal status at all, and in the National Health Service his supreme authority was confirmed by Statutory Instrument (S.I.) 419 (1948). Certainly, the medical superintendent then had little reason to see his authority threatened in any way. There were of course the newly formed medical advisory committees, but medical policy was usually channeled through the medical superintendent and expressed solely by him. He could personally make or mar his hospital and to some extent he still continues to be regarded, or regards himself, as the personification of his institution.

This somewhat idealised conception of the role of the medical superintendent was expressed in the W.H.O. expert committee's report on mental health.[2] "Whereas the individual psychiatrist, or nurse, will be occupied with therapeutic groups of patients, the therapeutic group with which the superintendent must occupy himself, is nothing less than the hospital community as a whole; the medical director will be unable to undertake this psychiatric task unless he carried the ultimate responsibility for all aspects of the therapeutic community." There was no hint in this report of the necessity of working in conjunction with senior and other medical colleagues.

The Bradbeer Report

Many witnesses in the Bradbeer report felt that the relation between a medical superintendent, his colleagues, and his committee, as affected by S.I.419 was the outstanding administrative problem in mental hospitals.

More consultants had been appointed under the National Health Service, and the result was to "convert the medical superintendent from the head of a clinical hierarchy to, at best, first among clinicians of equal status in mental hospitals".[3] Demand for consultation within the hospital had increased and the report said that "the powers and duties of a medical superintendent in relation to the patients might produce conflicts of opinion with individual consultants".[3] Nevertheless, witnesses from the Board of Control and the Ministry of Health, in defending S.I.419, felt that authority in medical hands was necessary to deal with day-to-day emergencies and that the medical superintendent should be able to intervene in *any* matter affecting a patient. Moreover, they saw "no need for difficulty between the superintendent and his consultant colleagues".[4]

For mental hospitals the Bradbeer report favoured the continuance of the medical superintendent. "The nature of the hospitals and the patients still demands the constant presence of someone in authority."[5] Moreover there were the legal duties and responsibilities of the hospital towards the patients. For general hospitals, on the other hand, a medical administrator should be appointed for a limited period from among the existing consultants by a committee composed of representatives from the medical staff committee, the hospital management committee, and the regional board.

It is not clear why this arrangement was considered unsuitable for mental hospitals; indeed, the procedure was recommended for certain mental deficiency institutions. A medical administrator appointed in this way could still discharge the quasilegal obligations and responsibilities of the mental hospital as capably as a medical superintendent.

Future of the Superintendent

Under the stimulus of the new Mental Health Bill, there has been a demand for clarification of the term "responsible medical officer" and for the repeal of the statutory instrument which gives the medical superintendent unlimited administrative powers. At present, the future of the mental-hospital superintendent is obscure. Some fear, and others hope, that the intention of the Bill is the removal of the medical superintendent from the mental hospital and his replacement as the chief officer by a layman. Some claimed that only the medical superintendent in his present form can save the hospital from the terrors of lay administration. Criticised as one who dominates committees and professional bodies,[6] the medical superintendent counters by asserting that "the carefully planned therapeutic environment can be maintained only if there is one individual within the community, and sensitive to its atmosphere, who is responsible for its control. There seems to be no reason why the medical superintendent, as primus inter pares, should not continue to function as chief officer of the hospital and to order its affairs in consultation with his colleagues so that an atmosphere suitable for their work can be maintained."[7]

The operative words, many will agree, are "in consultation with his colleagues". It is owing chiefly to this lack of consultation that, as one correspondent[8] affirms, "staff

1. Standing Committee E, Mental Health Bill, 11th sitting, p. 491. H.M. Stationery Office.
2. W.H.O. Expert Committee in Mental Health (3rd report), *Wld Hlth Org. tech. Rep. Ser.* no. 73, p. 24.
3. Ministry of Health: Central Health Services Council. Report of the Committee on the Internal Administration of Hospitals. 1954. H.M. Stationery Office.
4. *ibid.* p. 37.
5. *ibid.* p. 38.
6. *Lancet*, 1959, i, 578.
7. *ibid.* p. 517.
8. *ibid.* p. 471.

relations in many hospitals are virtually at the point of breakdown". This writer considers that not only is there no effective consultation, but interference by the medical superintendent with the admission and discharge of a consultant's patients is a commonplace, and he quotes instances where consultants have been refused the right to sign letters on their own behalf or sign death certificates on their own patients.

In the Scottish hospital system the medical superintendent is not allowed to engage in clinical work, because this could produce a bias towards certain specialties in treatment. The disadvantage of this policy would seem to be the depriving of a possibly keen clinician of clinical work. On the other hand medical superintendents are only human and one of the greatest dangers of interference comes from the keen and conscientious man who considers certain treatments of tremendous value and others as positively harmful. The very strength of his convictions makes it almost impossible for him not to interfere.

As an alternative there is support for entrusting much of the responsibility for administration in mental hospitals to medical staff committees. This is criticised on the grounds that the authorised chairman of the medical advisory committee will act as a superintendent in everything but name, and thus the debate reduces itself, according to one correspondent,[9] to whether the medical superintendent should be appointed by the management committee and regional hospital board, or by election from the staff. But the writer ignores the distinct advantages in an appointment in which all three bodies cooperate as recommended by the Bradbeer report. Such cooperation does ensure that the administrator is fully acceptable to his colleagues and much more likely to take them into consultation, which is surely the essence of good administration.

The Belmont Experiment

Background

Belmont Hospital was started in 1939 as an evacuation centre of the Maudsley Hospital and was organised largely on the administrative pattern of that hospital, with a medical superintendent, a deputy superintendent, a clinical director, and E.M.S. psychiatric specialists and medical officers.

The medical superintendent was in sole administrative charge with a position analogous to that of a superintendent in a general E.M.S. hospital. The senior medical establishment has always been a relatively large one and from the first there was little interference by the medical superintendent in the clinical freedom of his staff. The fact that the hospital was never subject to the Board of Control is important in this connection, and furthermore the legal supermacy of the medical superintendent was never applicable because the hospital was technically not a mental hospital. This is still the position, although the hospital has continued to treat a large and varied cross-section of psychiatric illness. Although officially a neurosis centre and separately designated as a special hospital, at least a quarter of the patient population suffers from psychotic illnesses and only the acutely disturbed and the very chronic and deteriorated have had to be excluded.

The Plan

The hospital is associated with St. Ebba's Hospital and a group medical advisory committee has taken a lively interest in medical administration with the support and encouragement of the medical superintendent. In 1957, when the former medical superintendent announced his intention of retiring, the group medical advisory committee proposed that, instead of perpetuating the post of physician-superintendent at Belmont Hospital, a medical administrator should be appointed, as recommended for nonteaching hospitals in the Bradbeer report. The retiring superintendent saw no objection to this proposal, but a special subcommittee of the hospital-management committee doubted whether a medical administrator could be the agent of the medical staff and at the same time obey the directions of the hospital-management committee. It thought that at times such an officer would suffer from divided loyalties. After further discussions, however, it was finally agreed to appoint a medical administrator for two years. The nominee of the medical staff committee was to be approved both by the hospital management committee and the regional board, on the understanding that he would in no way act as the agent or representative of the medical staff committee. In actual fact he was unanimously nominated by the medical staff committee, and quite clearly, if the administrator is to have a good working relationship with his colleagues, he must in large measure be their representative. Both we and our colleagues regret that in spite of subsequent correspondence the regional board has been unable to accept this point of view.

9. *ibid.* p. 472.

Results and Discussion

Near the end of the two years there is general agreement that the arrangement has worked well. It has been found both practicable and desirable to work in close consultation with senior medical staff, and the administrative structure which has been evolved is based on the medical staff committee. This committee, on which registrars are represented, meets regularly once a month, and designedly the chairman and secretary are not the medical administrator or his deputy. All relevant matters can be, and are, discussed. In addition there is a small subcommittee consisting of the chairman and secretary of the medical staff committee and the administrator and his deputy. This subcommittee meets weekly for about half an hour and formulates and clarifies points for the medical staff committee. There are also regular combined meetings of medical and nursing staff, and at these the opportunity is taken of ventilating difficulties and of discussing plans and schemes. Some may say that this is moving towards government by committee and that there is duplication and much encroachment on the time available for clinical work. Nevertheless, there is an indirect, but important, clinical aspect to all these activities, and it is generally thought that the time is well spent. Friction has been minimised, scope and opportunity widened, and above all a feeling engendered that the staff are actively participating in the life and work of their hospital. At the same time there is nothing in the procedure which undermines the medical administrator's direct responsibility to the hospital management committee and to the board. It could well be argued that with free and full consultation the relationship of the medical administrator vis-a-vis the hospital management committee is strengthened rather than weakened.

Both in and out of Parliament there has been wide support for a period of appointment longer than two years. The Bradbeer report itself recommended that the appointment should be for four or five years and should be renewable if circumstances dictated. This does seem to have advantages. It is a period which does ensure continuity of policy and effective planning, yet at the

same time it means that the medical administrator is not there to stay. There seems to be a real and inescapable need for one member of the senior staff to be responsible for coordination and planning, but his success will depend on the continuing confidence of his colleagues, both medical and lay.

Conclusions and Summary

We see the ideal structure of medical administration in the mental hospital as follows:

1. An adequate number of senior medical staff who enjoy complete clinical independence.
2. An active and fully representative medical staff committee or group medical advisory committee with a chairman and secretary who are preferably not the medical administrator or his deputy. Such medical advisory committees should have direct access to the hospital management committee.
3. A medical administrator and his deputy nominated by the medical staff and fully acceptable both to the hospital management committee and the regional board and appointed by agreement among all three bodies, with a period of office of four or five years and renewable if desired.
4. The medical administrator should be regarded as a representative of the medical staff committee as well as the representative of the regional hospital board and the hospital management committee.

As far as (3) is concerned, this works in practice and has many advantages, but, unfortunately, (4) has so far not been achieved at this hospital. Nevertheless, we regard the scheme as an innovation and a break from tradition. Understandably, fears and even suspicions have been encountered. Some members of the hospital management committee may have feared that the medical administrator would be transformed into the tool or agent of the medical staff and cease to be their officer and their sole channel of communication to the staff. On the other hand, a few senior medical colleagues may see it all as " the mixture as before " and continue to regard the medical administrator as a medical superintendent under a new name, in spite of his limited term of office and novel method of appointment. With a modicum of reason and good will we feel these doubts and fears can be allayed. It is very much in the interests of patients and staff to avoid anything which smacks of a dichotomy between the administrator, whether lay or medical, and the clinician. Evolving a satisfactory pattern of medical administration is a task of the highest importance, and the Belmont model and experience may well contribute to the answer.

This article is written at the suggestion of the medical staff committee of this hospital and with their full agreement. We thank them for their encouragement and support and for their many valuable comments. We should like also to record our appreciation of the hospital management committee and the regional hospital board, whose helpful and enlightened attitude throughout the discussions made this experiment in administration possible.

Points of View

VARICOSE VEINS

NATURE'S ERROR OR MAN'S?
Some Implications of the Darwinian Theory

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IN 1959, one hundred years after the publication of *The Origin of the Species*, Darwin's theory is still insufficiently applied to medicine. Varicocele, varicose veins, and femoral thrombosis are only a few of the many conditions on which it can throw new light.

The side of the Darwinian theory which chiefly concerns us is what may be called the law of adaptation, by which (through the struggle for existence with survival of the fittest) species adapt themselves to their environment. Since a species must adapt or perish, each species is perfectly adapted to the environment in which it has been evolved; but clearly an adequate period of time is essential for its adaptation to any unnatural—i.e., new—factor in its environment.

VARICOCELE

Nearly every textbook of surgery gives two alternative explanations of varicocele, which take into account the fact that it is much commoner on the left. The first is that the left spermatic vein opens into the left renal vein at right-angles, without a valve, whereas the right spermatic vein opens into the vena cava obliquely, with a valve. This difference, it is contended, leads to a greater pressure in the left spermatic vein and so to the development of a varicocele on the left side. In short, the spermatic vein is a natural " weak link " in the body, the weakness being accentuated in certain persons. The second explanation is that on the left side of the abdomen the iliac colon, often containing an accumulation of material, crosses directly over the left spermatic vein; whereas on the right side of the abdomen the cæcum does not cross over the right spermatic vein, and indeed is partly kept away from it by the larger mass of the external iliac vessels. This difference, it is suggested, leads to a greater pressure in the lower part of the left spermatic vein, and so to the development of a varicocele on the left side.

No-one guided by the Darwinian theory will give more than a thought to the first explanation. Application of the law of adaptation leads in fact to exactly the opposite conclusion—that, far from representing an error in mechanical conception, this difference in arrangement of the two spermatic veins is definitely necessary. The necessity presumably arises from the asymmetrical disposition of the viscera in the abdomen.

The second explanation, however, can be readily reconciled with the law; for, though under natural conditions the difference in the relation of the colon to the spermatic vein on the two sides *must be wholly compensated* in the total anatomy of the abdomen, under the suddenly new conditions of civilised life this difference can become important. Thus the removal today of so much of the fibre from foodstuffs often leads to delay in the passage of the colonic contents and hence to increase in their weight. Since a relatively low pressure can arrest the blood-flow in even the largest veins, a loaded iliac colon can easily obstruct the left spermatic vein, and ultimately induce a varicocele.

The fact that many people with varicocele would not admit to constipation counts for little. Many people suppose that their bowels are acting normally so long as they pass a stool each day, whereas the true criteria of normality are the diameter of the stool and its hardness (best shown by faceting), which increase steadily with delay. A person whose intestinal function is thought to be normal because the bowels always act every day may in fact always have twenty-four hours' delay, or more. Therefore, instead of seeking the cause of varicocele in a

crude constipation, we must seek it in delayed passage of the colonic contents.

VARICOSE VEINS

The usual explanation of varicose veins is that the veins of the leg, chiefly as regards their valves, are not yet adapted to Man's erect posture—that they are, in fact, a defect in the structure of the body, accentuated in certain persons. But this is quite untenable. How can we suppose that the evolutionary forces, which during untold ages have adapted Man's feet, hands, legs, and arms, and countless other structures, to the erect posture, have failed to make the necessary adaptations also in his leg veins? It is not as though varicose veins were rare, or confined to people above the reproductive age whose physical efficiency may be reckoned unimportant to the survival of the race. De Takats and Quint [1] found that 10% of 1000 otherwise healthy young workers suffered from varices of some degree, and in older people they are, of course, far more prevalent: for example, Foote considers that in Great Britain the number affected is in the region of 5 million, and it is now the commonest surgical ailment in this country. Such a tremendous incidence is evolutionarily quite incompatible with the view that the veins are a structural weak link—a failure in Man's evolution. The struggle for existence has never been so kind as to permit a state of affairs like this.

Some may argue that, being confined to certain individuals, varicose veins should rank as a congenital malformation. But congenital malformations are rare, most of them being found in well under 0·5% of the population, whereas varicose veins are more than twenty times commoner than this. Moreover congenital malformations are typically errors in the fusion of certain embryonic planes and not errors in mechanical conception.

The alternative view—that varicose veins, like varicocele, are attributable to pressure from an unnaturally loaded colon—has been put forward by anatomists [2] but attracts no attention. One reason for this is that ordinary varices are only about 10% commoner in the left leg than in the right,[3] and, though it is easy to see that on the left side the iliac colon, containing heavy fæces, could press on the external iliac vein, it is less obvious why the right external iliac vein should be obstructed by the cæcum, which is less directly related to it.

The explanation here appears to be that in the standing or sitting position the entire weight of the contents of the ascending colon, which are fluid, is transmitted down to the cæcum, and, if the colon is overloaded, this pressure will be considerable. A cæcum distended in this way, and well overlapping the external iliac vessels (as it commonly does), could therefore exert a greater pressure than does the iliac colon, which, although also unnaturally full, receives, through frictional considerations, no comparable transmitted weight from the contents of the descending colon, which are by now semi-solid, and in addition may be riding clear of the vessels through a lax arrangement of the commencing pelvic mesocolon. This explains why ordinary varices, when they occur in only one leg, occur only about 10% more frequently in the left than in the right. It is important to add that, owing to variation in the position and attachments of the colon and in the sites of any accumulations within it, even an overloaded colon may not press on either vein.

1. De Takats, C., Quint, H. *Surg. Gynec. Obstet.* 1930, **50**, 545.
2. Cunningham's Manual of Practical Anatomy (edited by J. C. Brash); vol. ii, p. 309. London, 1948.
3. Dodd, H. Personal communication, 1958.

FEMORAL THROMBOSIS

Varicose veins of severe degree, which have usually been preceded by femoral thrombosis, are commoner by about 50% on the left side.[3] Such thrombosis has nearly always arisen during an illness in bed, and is ordinarily attributed to recumbency; but recumbency does not explain why, as originally pointed out by Aschoff, thrombosis is considerably commoner on the left than on the right.[4–6] There is, however, no difficulty here, on the present view. I have pointed out that the varicose veins on the right side are the result of pressure on the right iliac vein by a distended cæcum—a cæcum distended, when its owner is sitting or standing, by the transmitted weight of the fluid contents of an overloaded ascending colon. During recumbency there will, therefore, be much less distension and pressure on the right side; but there will still be pressure on the left side where the iliac colon, loaded with semi-solid fæces, overlies the left iliac vein. Hence, arising during recumbency, femoral thrombosis is much more likely to occur on the left than is the case in ordinary varicose veins.

According to the law of adaptation, recumbency represents a risk only in so far as it is unnatural for human beings. It will be unnatural if, for example, unnatural nursing positions (such as Fowler's) are imposed, or if the patient is discouraged from natural fidgeting and change of position, or if he is actually prevented from making these movements (as in the treatment of certain fractures), or if he is too weak to make them (as in hemiplegia or profound asthenia)—in which case there may be venous stasis sufficient to result in a thrombosis. A study of Gibbs' paper [4] leaves no doubt that this unnatural type of recumbency is, indeed, a dominant cause of femoral thrombosis. But there is nothing in this view to exclude colonic stasis, of the type described, as being often a contributory factor, and sometimes a major one. During recumbency the speed of the circulating blood always falls greatly, and during unnatural recumbency it falls still more.[7 8] In such circumstances thrombosis may easily occur without any colonic obstruction to the veins, but it will occur still more easily if such obstruction is present.

PRESSURE AND FLOW

Thus for femoral-vein thrombosis, recumbency is usually required. Formation of varicose veins, on the other hand, requires the erect position. In this position, especially during walking and other movements, the speed of the circulating blood is much higher, and, even with colonic obstruction of the iliac veins, will prevent thrombosis. But such an obstruction, in conjunction with the increased flow, will result in a higher pressure on the walls of the veins, and this in turn will lead to "varicose" widening and lengthening in the walls of any veins not well supported by the surrounding tissues—i.e., the superficial veins. This process is furthered by secondary incompetence in the valves.

I must emphasise that the rise in pressure from colonic obstruction may be very small, and quite possibly intermittent at that. Hence one can readily understand reported failures to demonstrate any reduced rate of flow in the veins of one leg compared with the other.

Payling Wright and Osborn [9] made their observations on healthy subjects; and though these lived in this country, where the food is of the type liable to cause colonic stasis, such stasis would be marked in only a minority of them. Furthermore, in only a proportion of this minority would it interfere with the venous return from the legs; and in only a fraction of this

4. Gibbs, N. M. *Brit. J. Surg.* 1957, **45**, 209.
5. Barker, J. T. *Proc. Mayo Clin.* 1941, **16**, 1.
6. Atkins, H. J. B. *Guy's Hosp. Rep.* 1938, **18**, 92.
7. Wright, H. P., Osborn, S. B. *Lancet*, 1951, i, 22.
8. Wright, H. P., Osborn, S. B. *ibid.* 1952, ii, 699.
9. Wright, H. P., Osborn, S. B. *Brit. Heart J.* 1952, **14**, 325.

proportion would the interference be greater on one side, more usually the left. Therefore, to demonstrate that people living on a civilised diet tend to have a slower venous flow in the left leg would require an experiment of very large numerical proportions. Moreover, since the rise in pressure that produces varicose veins is so small that it takes many years to be effective, it would require an experimental technique of such delicacy as to appear quite impracticable.

As for the subjects in bed, it is easy to demonstrate the gross falls in venous flow that occur in certain types of unnatural recumbency, but it would be extraordinarily difficult to demonstrate any additional fall due to unnatural colonic obstruction. Though on this addition may depend the knife-edge decision whether thrombosis occurs or not, it may be too small to measure. Measurement has, however, never been attempted in cases of known colonic stasis.

At this stage I should point out that the law of adaptation positively precludes normal pregnancy from being a *primary* cause of either femoral-vein thrombosis or varicose veins, however much it may aggravate them.

DIFFERENCES BETWEEN INDIVIDUALS

Among people living in this country, with the same general environment and eating much the same food, some have varicose veins while others have not. No doubt this is because they differ in the robustness and valvular arrangements of their leg veins and in the arrangement of their colons. But in the absence of the primary cause—held here to be colonic stasis—these structural differences would not produce any disease at all. In the 1914–18 war tall men were shot down, during assaults against machine-guns, or by snipers when in the trenches, considerably more often than short men were; yet no-one looking at the dead body of a tall man killed in this way, whose father had been killed in exactly the same way in the Boer War, would consider the death primarily due to a structural difference (i.e., a difference in build), since in natural circumstances the extra height might have been an advantage, not a disadvantage. An exactly similar argument may be used against the view that varicose veins are due primarily to structural differences in the veins themselves.

Similarly, the accepted hereditary tendency to varicose veins falls into place. If there are structural differences between people, they are likely to be transmitted; and, when exposed to the same primary unnatural cause (colonic stasis), some families will develop varices more than others. But, according to the law of adaptation, the varices would not appear at all without this unnatural cause being present.

With perhaps 5 million sufferers in these islands alone, there is obviously little scope for any special incidence as far as occupation is concerned; and it is hardly surprising to find that at least one English authority [9] does not regard varices as more common in athletes, in people who stand a lot, or in the obese. Nearly all writers, however, agree that about three-quarters of the sufferers are women—who are known to suffer much more often than men from colonic stasis.

DIFFERENCE BETWEEN RACES

No proper investigation into the prevalence of varices in the different races has ever been made; but it has been vaguely recognised that the condition is relatively rare among non-Western peoples. Fortunately, it is possible to be much more precise in this matter in the case of Negroes living under truly primitive conditions in Equatorial Africa and Negroes living in the United States. In the former varicose veins and varicocele are hardly ever seen.[10] For example, Professor Croot and Mr. Cook of Makerere, mentioning a number of surveys in Uganda (dealing, among others, with the tallest and shortest races of humanity), say that "varicose veins and varicocele had never been noted in any of these tribal areas by any of the seven observers who have studied these peoples and must be considered exceedingly uncommon". But any suggestion that this freedom is due to a racial immunity can be discounted by the experience of Negroes in the United States, whose diet is much the same as that of the Whites. For example, Dr. C. Menedez of the vascular clinic at New Orleans, tells me that in his opinion the incidence of these conditions there is the same for the two races, and the admissions to the Charity Hospital show how common these conditions are in the Negroes in the United States.

As I need hardly say, the remarkable difference in prevalence of varicose veins between civilised and uncivilised races presents no problem to a holder of the view I am advancing, but is a perpetual challenge to those who attribute varices to some error of Nature.

EVIDENCE FROM THE PAST

Hippocrates and his school, around 450 B.C.,[11] referred to varices and their treatment; and some may ask why, if they are due to colonic stasis, resulting from the food of civilisation, they were described as long as several thousands of years ago. The answer lies in the fact that Man has existed for nearly a million years, and that for about half this time he has been sufficiently advanced to be able to light a fire and heat food over it.[12] Such an epoch is 100–200 times the length of recorded history, of which it makes but a thing of yesterday. The argument is as follows:

The evidence we can get from prehistoric times must be indirect; for, though some of the bones of prehistoric men remain, their soft tissues have long since disintegrated. But a parallel can be drawn between varices and another disease of civilisation—caries of the teeth. The kind of caries so prevalent today is, like varices, virtually absent from the few surviving primitive races, but, like varices, is described in the writings of very ancient civilisations. Since teeth often survive burial, we can in their case actually trace the rise of caries through historic times. Thus of 32 skulls of Britons about 1500 B.C., 7 already showed caries [13]; in 38 Londoners of the 17th and 18th centuries, the figure had risen to 26 [14]; and nowadays, of course, almost any skull would show extensive caries—if it contained any teeth at all. (How fortunate it is that there is at least one disease whose implications cannot be evaded by saying that "it was just as common in the past, only it was never diagnosed"!)

There are few writers on the history of dental caries who do not think that, though the disease bears some relation to the introduction of the practice of cooking food, its main march has been with the increasing removal of fibre in the refining of carbohydrates.[15] To suppose that this refining of cereals is of very recent origin is a mistake.

Apart from much earlier evidence from Egypt, we know that white flour was being produced in Greece at least as early as 500 B.C. and Hippocrates himself recommended white bread for a patient with diarrhœa, thereby showing that it was already known to pass through the gut at a reduced speed.[16] In Britain,

10. Personal communications from Prof. H. J. Croot and Mr. J. Cook of Makerere College, Uganda; Dr. J. D. B. Longley of Queen Elizabeth Hospital, Umuahia, Eastern Nigeria; Dr. D. G. Milton-Thompson, of Edwards Memorial Hospital, Mombasa; and Miss E. T. Mess, of Wasasa Hospital, Northern Nigeria.
11. Anning, S. T. *in* Dodd and Cockett's Pathology and Surgery of the Veins of the Lower Limb. Edinburgh, 1956.
12. Le Gros Clark, W. E. History of the Primates; p. 82. London, 1950.
13. Colyer, J. F., Sprawson, E. Dental Surgery and Pathology, p. 317. London, 1953.
14. Colyer, J. F., Sprawson, E. *ibid.* p. 318.
15. Colyer, J. F., Sprawson, E. *ibid.* p. 386.
16. McCance, R. A., Widdowson, E. M. Breads White and Brown. London, 1956.

at any rate from the Roman occupation, the flour was ever more frequently sieved to remove the bran. By the end of the 17th century some of the poor were eating it, and by the end of the 18th almost everyone was doing so.[16]

The increase in the consumption of refined sugar, derived from the sugar-cane and sugar-beet, is much more recent. Reaching England in the 12th century, refined sugar remained a food of the rich for a very long time. Since 1815, however, consumption has risen from 15 lb. per head per annum to over 100 lb. today.[17 18]

If one disease produced by the refinement of carbohydrates—dental caries—can be seen already to have become noticeable in the earliest civilisations, there is no reason why another, such as varicose veins, if due to the same cause, should not have become noticeable too; and the description of this disease by Hippocrates therefore presents no obstacle to the view advanced here—though, needless to say, in those days the disease must have been very much rarer.

VARICES ELSEWHERE THAN IN THE LEG

My argument is that the primary cause in every case of leg varices is slowing of the passage of the contents of the colon, due to the removal of fibre from the food. Any other factors, such as inherited structural differences in the veins themselves, and pregnancy, do no more than aggravate this primary cause, and without it have no effect whatever.

The mechanism I suggest for varices in the legs is no more remarkable than the mechanism already accepted for hæmorrhoids (varices in the rectum), the only difference being that in hæmorrhoids the pressure of fæces is exerted on veins inside the gut, whereas in leg varices this pressure is exerted on veins outside it. Varicocele, and varicose veins of the vulva (in which an overloaded gut, usually only during pregnancy, affects, among others, the spermatic veins and the pudendal branches of the internal iliac veins), belong to the same group. It is highly significant that, except for those due to known specific causes (e.g., œsophageal varices in cirrhosis of the liver), all varices are confined to those limited areas in which pressure from the colon can account for them.

SUMMARY AND CONCLUSIONS

Orthodox opinion holds Nature primarily responsible for varicose veins. Her design of the veins of the human leg (it is supposed) did not stand up to the strains arising when Man adopted the erect posture a million or more years in the past. This is nonsense. Like all other species, Man was perfectly adapted, in structure and function, for the environment in which he always lived until only a few thousand years ago. Varices are one of the consequences of rapid alteration in that environment. They are very rare in races still living under primitive conditions, but very common in those which have undergone civilisation. This equally affects the view that varicose veins are due to a congenital abnormality.

The evidence reviewed here suggests that the environmental change responsible for varices is the adoption of a diet largely freed from vegetable fibre. In many people the effect of such a diet is to slow the passage of food residues through the colon. Such slowing is compatible with regular action of the bowel, but it causes overloading of the colon. This process affects the venous return from the lower parts of the body.

During enforced recumbency, slight and intermittent compression of the external iliac veins by a colon weighted in this way may tip the balance towards femoral-vein thrombosis. In people who are standing or sitting it can and does lead to varicose enlargement of the veins of the leg. The latter mechanism is not fundamentally different from that already accepted in the case of hæmorrhoids.

Is the body built wrongly, or is it built rightly but being used wrongly? That is the question, and it can be applied to more than one important disease today; but in a country where the widespread use of aperients is a convincing testimony of the degree to which the food is being refined, there should be little difficulty, as far as varicose veins are concerned, in seeing which answer is the correct one.

I am grateful for very real help from the authorities quoted, especially to Mr. J. Cook, and to Mr. Harold Dodd for his assistance and encouragement throughout. The argument presented is being published shortly in considerable elaboration.

17. Fairrie, G., Sugar. Liverpool, 1925.
18. *Board of Trade J.* Aug. 11, 1956.

Public Health

PARATHION POISONING INCREASING FREQUENCY IN FINLAND

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THE use of parathion as an insecticide started during the second world war. It was first sold in Finland in 1950, and by 1957 the total of parathion preparations sold had risen to 160 tons. Nearly two-thirds of all pest extermination on farm and garden now employs pesticides containing parathion (Roivainen 1958).

In the human body parathion (diethyl-nitrophenyl-thiophosphate) inactivates cholinesterase and the resulting rise in acetylcholine concentration stimulates the parasympathetic nervous system and peripheral nerve endings (Moeschlin 1952).

Parathion may cause poisoning when it enters the body through the mouth, the respiratory organs, or the skin. In man 200 mg. of parathion by mouth has caused death (Goldblatt 1950), and a single drop of parathion in the eye may have a fatal effect (de Ong 1956). Death usually follows in $^1/_2$–4 hours but occasionally within a couple of minutes (Kaye 1954).

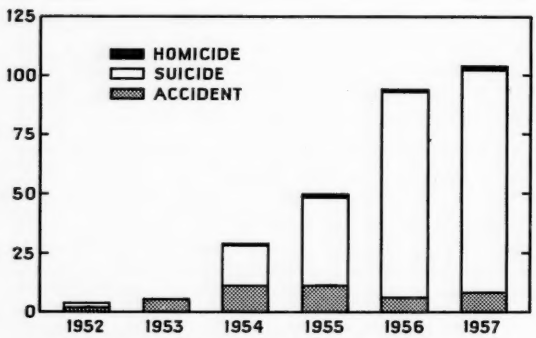
Parathion is used as a herbicide as a dusting powder (parathion content 1·5–2·5%), as a spraying powder (parathion

TABLE I—FATAL CASES OF POISONING BY PARATHION, 1952–57

—	1952	1953	1954	1955	1956	1957	Total
Homicide ..	0	0	1	2	1	3	7
Suicide ..	1	0	17	37	88	94	237
Accident ..	1	5	11	11	6	8	42
Total ..	2	5	29	50	95	105	286

TABLE II—AGE-DISTRIBUTION OF FATAL CASES OF POISONING BY PARATHION

Age (years)	0–9	10–19	20–29	30–39	40–49	50–59	60–
Homicide ..	2	5	0	0	0	0	0
Suicide ..	0	13	43	55	65	51	10
Accident ..	27	1	3	3	4	3	1
Total ..	29	19	46	58	69	54	11



Mortality from parathion poisoning in Finland, 1952–57.

content 5–15%), or as a liquid spray (parathion content 25–40%) (*Kasvinsuojeluaineluettelo* 1958).

Our data are taken from the records of the Central Statistical Office for Finland. The results are shown in tables I–III.

In Finland between 1952 and 1957 286 people were killed by pesticides (nearly all of them containing parathion). The incidence has increased year by year (see figure and table I), but the use of parathion for suicide has increased disproportionately.

In Denmark, also, mortality from parathion shows similar features (Karlog et al. 1958) (table IV).

In Denmark in 1956 13 people killed themselves by taking parathion (we do not know the number of cases of accidental poisoning for the same year), while the corresponding figure in Finland was 88 cases in the same period. In Finland in 1956 the number of suicides with parathion were already more numerous than suicides with hypnotics, then about 40% of total suicides by poisoning (table III).

TABLE III—ANNUAL TOTAL OF SUICIDES WITH PARATHION COMPARED WITH SUICIDES WITH HYPNOTICS AND BY POISONING

—	1952	1953	1954	1955	1956	1957
Suicides with herbicides ..	1	0	17	37	88	94
Suicides with hypnotics ..	58	53	68	72	80	98
Total of suicides by poisoning	102	99	159	175	234	247

TABLE IV—PARATHION POISONING IN DENMARK, 1953–56

Year	Suicides and attempted suicides	Accidental poisoning
1953	1	11
1954	4	19
1955	3	15

Most of the accidental deaths were in small children (table II). The poison was usually taken by them either because in ignorance they tasted the substance carelessly left within reach, or because a parathion preparation was given by mistake—e.g., as a cough mixture. In adult accidents the reason in some cases was alcoholic intoxication, in others parathion had been taken for a cough. A total of 7 people were poisoned by parathion in the last mentioned way during the period reviewed.

We have also inquired into the occupation of patients who died from parathion poisoning. Of these, 43 were farmers, agricultural labourers, or members of their families, and 13 were skilled horticultural workers. Hence 56 (i.e., 20%) of the fatal cases had had an opportunity of and need for acquiring parathion for their work. The remaining 80% acquired the poison by other means but evidently found little difficulty in buying it.

To obtain an idea of the significance of the number of fatal cases due to parathion pesticides, we can mention by way of example that in Finland pregnancy, parturition, and puerperal complications were the cause of death of 94 persons in 1955, 99 in 1956, and 77 in 1957. Again, deaths from poliomyelitis in 1956, when mortality from this disease was at its highest, were 37.

Summary

In Finland between 1952 and 1957 there were 286 deaths from parathion pesticides used in agriculture and horticulture. In 1957 the number had risen to 105. 237 of the total deaths were by suicide.

Only 20% of these cases had an opportunity of procuring the poison for their work. The sale of parathion preparations should be more strictly controlled.

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Recommendations for Arsenic Spraying

The Government regard the application of arsenites to any edible crop as undesirable on general grounds.[1] If potato haulms have to be destroyed and the use of some less toxic alternative is impracticable, every possible precaution should be taken. "On present information the use of alkali arsenites as a haulm-killer on potatoes should present no hazard to consumers"; but the Ministry of Agriculture's recommendations are designed also to protect "livestock, wild life, and others" from risks which have been causing concern.[2–5] The Ministry advises that employers should make sure that their workers know of the precautions to be taken, and that all users should follow the maker's instructions carefully. Children and cattle should be prevented from entering potato fields, both during and after spraying, and warning notices should be put up. Workers should avoid spilling the spray or contaminating nearby fields. The circular emphasises the danger of contaminating ponds and streams, and recommends that any surplus spray should be emptied into a pit dug to avoid its soaking away into water-supplies.

1. Ministry of Agriculture, Fisheries, and Food: circular FSH 6/58, revised July, 1959.
2. *Lancet*, 1957, ii, 1047.
3. Whitehead, T. P. *ibid.* p. 953.
4. Parker, W. H. *Agric. Rev., Lond.* August, 1958.
5. *Lancet*, 1959, i, 721.

Infectious Diseases in England and Wales

Disease	Week ending July			
	4	11	18	25*
Diphtheria	20	11	6	2
Dysentery	838	680	649	596
Encephalitis:				
Infective	4	3	3	—
Post-infectious	3	2	3	4
Food-poisoning	222	293	421	246
Measles, excluding rubella ..	10,132	8814	8552	7080
Meningococcal infection	17	15	16	21
Ophthalmia neonatorum	10	23	20	30
Paratyphoid fever	4	5	10	4
Pneumonia, primary or influenzal	180	158	178	168
Poliomyelitis:				
Paralytic	31	31	21	35
Non-paralytic	22	16	22	18
Puerperal pyrexia	199	200	192	221
Scarlet fever	902	784	781	804
Smallpox	—	—	—	—
Tuberculosis:				
Respiratory	497	448	447	415
Meninges and C.N.S.	1	8	8	6
Other	60	54	52	63
Typhoid fever	4	3	3	5
Whooping-cough	699	631	688	694

* Not including late returns.

Conferences

ASSOCIATION OF PHYSICIANS OF EAST AFRICA

THE annual conference of the Association was held in Kampala under the presidency of Dr. P. W. HUTTON on June 18–20.

Nitrofurazone in Rhodesiense Sleeping-sickness

Dr. D. H. H. ROBERTSON reported some unfavourable reactions to nitrofurazone in the treatment of trypanosomiasis. Manifestations in the acute stage were profound weakness, hypotension, and loss of weight during the first three days; sometimes also vomiting, anorexia, and oliguria were seen, and in a single case hæmolytic anæmia had occurred. When the disease had been controlled paræsthesiæ and pain of polyneuritis might develop nine to fifteen days after the start of treatment. Hypotension and tachycardia were also found in this stage. After withdrawal of the drug, symptoms usually diminished rapidly, but sometimes serious deterioration occurred after the patient had returned home.

Thiamine, if given early, produced rapid improvement in the condition, but was of little value when the condition was well established.

Dr. R. H. KNIGHT said that nitrofurazone has been shown to inhibit a number of bacterial enzyme systems and to interfere with the formation of acetyl coenzyme A from pyruvate and coenzyme A in certain mammalian tissues. Among the side-effects of the drug noted in mice had been signs of vitamin deficiency.

During the treatment with nitrofurazone of patients with *Trypanosoma rhodesiense* sleeping-sickness a study was made of blood-pyruvate concentrations at intervals after the administration of a loading dose of glucose. In 6 of the 7 patients studied who had received 15 g. of nitrofurazone in ten days, abnormally high pyruvate concentrations were found during the course of these pyruvate-metabolism tests. In no case was any deterioration in pyruvate metabolism found after 1·5 g. of the drug had been administered on each of three successive days.

By giving initially 50 g. of glucose followed by 15 g. of glucose every thirty minutes to a patient who showed an abnormality in pyruvate metabolism a high blood-pyruvate concentration, which remained constant over three hours, was produced. The administration of vitamin B caused a reduction of this high concentration to nearly normal values within two hours, although the patient continued to take 15 g. of glucose every thirty minutes. This finding is in agreement with the conclusions from clinical observations that nitrofurazone induces a condition of vitamin-B deficiency in man.

Isoniazid Neuropathies in Malnourished Tuberculous Patients

Dr. G. L. MONEY had surveyed the neurological disturbances among 84 ambulant tuberculosis patients in Ibadan on chemotherapy (isoniazid 4–6 mg. per kg. body-weight per day). This revealed an incidence of polyneuropathy and burning feet with objective physical signs in 16 patients after periods of treatment ranging from six to twelve months. A clinical classification of isoniazid neuropathies encountered in routine clinical practice at Ibadan included the burning-feet syndrome, peripheral neuropathy, myelopathy, encephalopathy, and a neurasthenic syndrome. Dietary supplements were not routinely provided for these patients. The high incidence of severe neurological damage compared with patients in socially advanced countries, the relief of symptoms on withdrawing isoniazid and/or adding vitamin supplements, the economic difficulty of providing adequate nutrition for the vast majority of tuberculosis patients in the tropics—all these point to the necessity for routine cheap vitamin B supplements (e.g., brewers' yeast), especially when high dosages of isoniazid are prescribed.

Dr. HUTTON said that in the high-dosage isoniazid trial they had seen no cases of myelopathy and only occasional minor mental disturbances. These appeared to be associated with a great gain of weight, presumably due to water retention. Prof. D. B. JELLIFFE discussed some work done in the U.S.A. on the rate of acetylation of isoniazid in different subjects, which may in part explain the varied clinical pictures produced. He mentioned the effect of pyridoxine in upsetting the balance and in precipitating the manifestation of vitamin-B deficiencies.

Phonocardiographic Findings in Endomyocardial Fibrosis

Dr. K. SOMERS had made a phonocardiographic study of 14 cases of endomyocardial fibrosis with atrioventricular incompetence, including 4 with both mitral and organic tricuspid incompetence. The usual graphic record is a pansystolic murmur with quadruple rhythm. The murmur, usually of high pitch, is not distinguishable from that of pure atrioventricular incompetence due to rheumatic heart-disease. Pure mitral incompetence is, however, more characteristic of endomyocardial fibrosis than it is of late rheumatic heart-disease. The occurrence of both diastolic sounds in nearly all cases, and the frequent association of the fourth sound with a mitral P wave in the electrocardiogram were noted.

In the discussion which followed it was admitted that the phonocardiogram alone could not differentiate endomyocardial fibrosis from rheumatic carditis or, indeed, from other forms of cardiac failure, but it could give an accurate record of the heart-sounds, including the third and fourth sounds when present, and differentiate them from diastolic murmurs.

Primary Lymphosarcoma of the Heart

Dr. SOMERS and Dr. F. LOTHE described 3 cases of primary malignant lymphoma of the heart occurring in Africans. All 3 cases presented with cardiac failure and in all 3 the diagnosis was made at necropsy. 1 patient died from cardiac tamponade with hæmopericardium, the other 2 from myocardial failure. In 2 cases pedunculated tumour nodules projected from the right atrium through the tricuspid orifice. Histologically the cases were classified under the lymphosarcoma group. Dr. SOMERS and Dr. LOTHE had found that the necropsy incidence of primary malignant tumours of the heart at Malago Hospital, Kampala, was 0·06%.

The Kampala Cancer Register

Prof. J. N. P. DAVIES said that the Kampala Cancer Survey (which was organised by the Cancer Research Committee of the Medical Faculty and financed by the British Empire Cancer Campaign) covered all the hospitals in Kampala, as well as all the ancillary diagnostic departments. He believed that virtually all cancer cases seeking medical aid were registered. Particular care was required to obtain details of the patients' age and address and this was done by the cancer registrar and by the social worker. As data from the East African Censuses became available it would be possible to provide minimum cancer incidence figures.

Dr. O'CONOR drew attention to some features of malignant tumours in children, as recorded at the Cancer Registry during its seven years of existence. In 125 cases the diagnosis had been confirmed by biopsy and/or necropsy. These tumours were classified according to histology, and compared with three large series from the U.S.A. by percentage of total tumours recorded. Significant differences were limited to a much lower percentage of leukæmia and a much higher incidence of lymphosarcoma (almost 50% of the malignancies in this study) in the Kampala series as compared with the others. This suggests a possible variation in the natural history of the tumours of the lymphopoietic system. Many of these lymphomas presented as massive jaw tumours and this is certainly a feature unique in Africa and indicates a local causative factor. Epidemiologic studies are in progress to elucidate this problem further.

The Widdicombe File

LV.—ANY OLD IRON?

MY DEAR WHIDDON,

You will remember that the Hospital Committee, at the request of the R.H.B., asked me to inspect and report on the autoclaves in our group of hospitals. I have found the experience most interesting—and terrifying. Since the result of any failures in this department is likely to be blamed on the surgeons you may like to hear what I found. (E. and O.E.)

Two Bridges Cottage Hospital has a small gas-heated vertical autoclave in an annexe of the theatre. Fundamentally it's no more than a pressure cooker. It has no thermometer but what the Matron (who operates it herself) calls " the clock "—i.e., a pressure gauge. When I saw it this had been stuck at zero for several weeks in spite of all the efforts of the local plumber. Whatever goes into the machine is heated—I would not say sterilised —" for about an hour " and comes out soaking wet. It is then returned and heated for another two hours with the lid off to dry it. As a result the turnover is small and all maternity dressings are baked in biscuit tins in the kitchen oven. (The genital tract is relatively resistant to infection.)

Postbridge Hospital.—This is a modern version of the machine at Two Bridges bought only two years ago by the hospital secretary without advice from anyone. It cannot draw a vacuum, it has no thermometer, and it's far too small for the needs of the hospital. But steam does at any rate penetrate downwards, and, as judged by the indicator tubes, it is reasonably efficient in the hands of a porter who follows the makers' directions to the letter. A pity that it's in a room which, if you housed a dog in it, would invite a prosecution from the R.S.P.C.A.; and even more of a pity that the drums when removed are left to share a corner with the dustbins.

At *Dartmeet and District Hospital* there are two very old autoclaves similar in design to those which I have described but in the charge of an intelligent theatre orderly —the only person I met who had some idea of the workings of an autoclave. In theory they draw a modest vacuum— or did so once upon a time. The orderly tries to sterilise dressings at 15 lb. and gloves at 10 lb.; but the only possible adjustment is by means of the main gas tap and the results are chancy. Indicator tubes are used in every drum and every drum is labelled and dated. Alas, some booby installed these machines in the theatre, and when the safety valves blow nothing else can be heard. Some of your surgical colleagues object to their words of wisdom being lost in clouds of water vapour, and so the sterilising is done at night as far as possible—and then the patients complain about the din.

St. Pirran's Home, Manaton.—This is the electric counterpart of the machine at Postbridge. This method of heating makes for easier automatic control but far slower heating—about two hours from cold. Luckily it is used only twice a week at the most. At one time they used indicator tubes but they've now abandoned them for reasons which they've forgotten.

Willhays Chest Hospital.—Here we come to bigger stuff, a horizontal machine fed by an adequate steam supply from the laundry. Of its history I could learn only that it had been " surplus ", and that's what it should be here and now. The designer seems to have made every error within the compass of human imagination. The steam, loaded with moisture, is led into the side of the chamber and most of it emerges from the safety valve on top. There is, of course, no air filter, and the only evidence that it draws a vacuum is that the needle on the gauge is stuck on the negative side. There is a dial thermometer which is a patent liar but there's no means of checking its inaccuracies. The porter-cum-laundryman who does his best with it tells me that he has to heat everything for 50 min. if the indicator tubes are to change colour.

Hexworthy Hospital (if you can stand any more).—This is a medium-sized model of a sound horizontal pattern worked by main steam: it was installed in 1923 and has been modified only by continuous neglect. It lacks air filter, near-to-steam trap, thermometer, and enough operating space; but all these faults could be remedied at small cost. It's the operator who is incurable. He is a neat and orderly fellow—the salvias are bedded in rows like guardsmen—and obviously obliging because I found him decarbonising the Matron's moped in the autoclave room; but his ignorance of the processes of sterilisation is absolute. It is really too dangerous to let one man take all the responsibility for the autoclave, the boilers, and the garden, with a few spare hours spent in driving the van and peeling potatoes. Luckily the autoclave makes the least demands upon his time.

And lastly there is the big autoclave at the *Widdicombe Hospital.* It is a splendid example of British engineering at its best and worst. The design has been essentially the same for fifty years. It will outlast all of us and has never failed to work after its own fashion. It is properly installed, with " clean " and " dirty " sides; but both rooms are indistinguishably sordid. The jacket pressure is twice that in the chamber and steam is discharged at 20°F. below the working temperature. It has an air filter in which no-one has put cotton wool within living memory. There is a massive recording pressure gauge but no thermometer, and I suspect that it's a long time since steam penetrated a load of dressings satisfactorily. Only too often the indicator tube in the centre of a drum fails to change colour and the Matron complains that pillows emerge wet and stained. The engineer will remedy the minor faults of construction in his own good time; but who is to supervise the daily tasks of the well-meaning but rather idle porter who operates the machine? The secretary wants notice of that question. The head porter says that the man is on Matron's staff. Matron declines the honour. The theatre sister told him that the drums were dirty and he broke off diplomatic relations. And so he remains an autonomous body, working the autoclave in accordance with some rather illiterate manuscript instructions which he inherited from his predecessor and impervious to any comments on indicator tubes or wet pillows. I am probably the first person who noticed on the evidence of the pressure gauge that it is very seldom that he sterilises more than two loads a day. The rest of his time is devoted I think, to cups of tea and meditation.

That's the picture, and I hope that you won't say that it really cannot matter much because there are few hospital infections. I'm not even sure that this is true; but until we can agree on how these infections should be recorded all our answers are guesses. I do hear complaints from G.P.s that too many patients are discharged with

suppurating wounds. I do know that in a court of law I would find it a strain on my conscience to say that the disinfection processes in use are as good as they could be. It's many years since the surgeons saw a patient with tetanus, but . . .

No, these autoclaves should be improved or scrapped; and I'm going to suggest immediate and long-term plans to this end. For the first it's essential that one person, a doctor or a nurse, be responsible for the autoclaving in each hospital. I don't mean that he (or she) should have to carry the drums or turn the knobs; but there must be one person, appointed officially, who will check the indicator tubes and complaints about wet dressings and take responsibility for remedying defects. In even the smallest hospital the machine should be inspected and serviced regularly by a trained engineer. Those who work them should be trained for the job. And lastly it should be obligatory to use an indicator tube in every drum in all these second-rate machines.

In the long run it'll be wise to centralise all the sterilisation at the Widdicombe Hospital. I've suggested certain improvements to the machine there, and if an electric evacuation pump be added we should have a machine able to do all the work of the group. A new machine will cost five times as much but has the advantage that even the most stupid operator will find it difficult to make a mistake. In either case the cost will be less than that of re-equipping six small hospitals with new autoclaves which will for the most part be used seldom and no more intelligently than those which they have now. The secretary tells me that the transport of drums hither and thither presents no problems at all; but we shall, of course, need more of them. At the moment I'm trying cardboard boxes as a substitute, and so far they seem to be satisfactory—and about a fiftieth of the price.

I know that there are moral dangers in centralisation—a loss of responsibility and so on. I already hear warnings of fallen trees, icy roads, and atomic fall-out. But though some of us tie our own flies we no longer make our rods as Walton and his friends did—and we probably get better sport.

Yours sincerely,
HARRY HAWKE.

P.S.—You'll have read the report of Professor Howie's committee on autoclaves in *The Lancet* of February 28. After my explorations in darkest Dartmoor I have the impression that the committee moved in very refined circles.

Medicine and the Law

Intention to Desert

A WIFE, after a difficult confinement, suffered from a neurosis which produced in her an invincible repugnance to sexual intercourse. She was admitted to a mental hospital as a voluntary patient where she was under the care of a psychiatrist from October, 1952, to June, 1956. She made efforts at rehabilitation by returning home from time to time on the footing that there should be no sexual intercourse, but after June, 1954, did not return again, and the psychiatrist told her husband that her condition was incurable.

She rejected her husband's requests to her to return, stating that "from a medical point of view" it was impossible and always would be. The husband thereupon ceased to maintain her; and she applied to the magistrate's court for maintenance on the ground that he was guilty of wilful neglect to maintain her. The psychiatrist gave the only medical evidence, which was uncontested, that her condition was neurotic rather than psychotic, that she was rational except in relation to her husband and other men, but that she would risk grave consequences to her mental health if she returned to her husband at the present time. The wife also gave evidence and her letters to her husband were before the magistrate.

The magistrate found that because of her neurosis the wife would risk grave consequences to her health if she returned to her husband, but he dismissed her summons, holding that, as the husband had not been guilty of matrimonial misconduct, he was not legally liable to maintain her, and that she was in desertion because on the evidence she was capable of making a rational decision, and of forming an intention to desert.

She appealed to the Divisional Court of the Divorce Division, which held that the husband was not legally liable to maintain her, but that she was incapable of forming the intention to desert. She appealed to the Court of Appeal, which dismissed her appeal.

Lord Justice HODSON, reading the judgment of the court, said that there was in this case a defacto separation in which the wife maintained that if the husband did not maintain her apart from him he was guilty of wilful neglect to maintain, just as much as if she were separated from him by necessity, such as the obligation of his profession. Their Lordships saw no reason why the husband's obligation to maintain should be affected by an enforced separation if it was forced on the parties by illness which compelled residence in hospital, whatever the nature of the illness, even if it were mental disorder, provided always that the intention of the absent spouse to return to the other continued; and accordingly if the wife here were not in desertion the husband must be guilty of the offence with which he was charged.

But accepting the finding as to the grave consequences to the wife if she returned to her husband now, the fact remained that on the evidence this wife was capable of making a rational decision to desert.

The *animus deserendi* had to be inferred from the words and conduct of the deserting spouse. The attitude of this wife went far beyond saying "I cannot return to you at present". She added in effect "and I never will". That had all the appearances of a rational conclusion. She was not a person of unsound mind. She had made a deliberate choice for all time, and could not properly complain of the natural consequences of her act. This was no doubt a strong case, for the neurosis of the wife was severe and might be incurable. It might appear hard, therefore, that she should be guilty of desertion if she expressed herself as unwilling ever to return to her husband; but the conclusion that she was in desertion was inevitable on the evidence as it stood. There was support for the view of the Court in Leng *v.* Leng,[1] where the Divisional Court had emphasised that the neurotic condition of a husband and nothing more was not in law sufficient ground for a wife's refusal to live with him. It had there been pointed out that, unless that were so, the ultimate result of a justice's order might in effect be a divorce on the ground of neurosis.

In this case the court did not think that the neurotic wife could in law justify a refusal ever to return to cohabitation. She was in desertion, and her appeal must be dismissed.

LILLEY *v.* LILLEY. *Court of Appeal* (Hodson, Sellers, and Harman *L.JJ.*); July 30, 1959. Counsel and solicitors—Rudolph R. Lyons, Q.C., and R. H. Hutchinson (Dawson, Loncaster & Co., Hull and London); W. A. L. Raeburn, Q.C., and Keith McHale (Smith & Hudson for Williamson, Stephenson and Hepton, Hull and Beverley).

M. M. HILL
Barrister-at-Law.

1. (1946) 2 All. E.R. 590.

"Incurably of Unsound Mind" Redefined

In May, 1952, a husband with paranoid schizophrenia entered a hospital, having been certified insane, and remained there. By her petition of February, 1958, the wife sought a decree nisi of dissolution of the marriage under section 1(1)(d) of the Matrimonial Causes Act, 1950, on the ground that the husband was incurably of unsound mind and had been continuously under care and treatment for a period of at least five years immediately preceding the presentation of her petition. In October, 1958, the husband, by the official solicitor as his guardian ad litem, filed an answer in which he denied that he was incurably of unsound mind.

At the hearing the medical superintendent of the hospital gave evidence that the husband still had delusions and hallucinations, but under recent treatment with 'Largactil' and other drugs he had improved so much that it was possible to consider his future discharge, provided that suitable living conditions could be found outside the hospital. Evidence was also given by two consultants who had examined the husband.

Mr. Justice PHILLIMORE said that largactil had effected an astonishing change in the treatment of schizophrenia and even in chronic cases a remarkable degree of recovery had been maintained The doctors who had given evidence agreed that, although in the light of present medical knowledge, there was no prospect of a full clinical recovery, some degree of social recovery, resulting in a discharge from hospital, perhaps at about Christmas, 1959, was not impossible if suitable living conditions could be found. Regular and continued dosages of the drugs would be necessary. The question to be decided was whether, on that evidence, the wife had discharged the burden of proving incurable unsoundness of mind. His Lordship had been pressed to define the term "incurably of unsound mind", since the emphasis on detention and consequently certification as a test had been removed by section 1 of the Divorce (Insanity and Desertion) Act, 1958, and since the official solicitor was greatly concerned at the number of divorced people who had as a result of further treatment later left hospital fit to resume normal married life.

His Lordship said that in using the phrase "of unsound mind" in the Act of 1950 Parliament must have intended to enable one spouse to obtain a dissolution of marriage when the mental incapacity of the other spouse, despite five years' treatment, was such as to make it impossible for them to live a normal married life together and when there was no prospect of any improvement in mental health which would make it possible for them to do so in future. The state of mind envisaged was, accordingly, a degree of unsoundness or incapacity of mind properly called insanity. If a practical test of the degree were required, it was to be found in section 90 of the Lunacy Act, 1890, "incapable of managing himself and his affairs" provided that it was remembered that "affairs" included the problems of society and of married life and that the test of ability to manage affairs was that to be required of a reasonable man.

What effect was to be given to the word "incurably"? If a man could hope to resume a normal married life and to manage himself and his affairs, no ordinary person would describe him as incurably of unsound mind because he had to take a drug regularly. Equally, however, if, in the light of medical knowledge at the time, the best that could be hoped for was discharge to conditions where he would not be required to manage himself and his affairs, but would live an artificial existence protected from the normal incidents and problems of life he would properly be termed incurable. A parallel in the physical sphere would be a patient who could go home but would always be bedridden.

The test to be applied was, therefore, whether the respondent spouse was capable of managing himself and his affairs and, if not, whether he could hope to be restored to a state in which he would be able to do so—the capacity to be required being that of a reasonable person.

The effect of the medical evidence in the present case was that there was no hope of more than a partial recovery, enabling the husband to live as the subject of sympathetic supervision and care. There was no real prospect of a return to normal life or normal married life where he would be able to manage himself and his affairs. He would be apathetic and lacking in volition and unfit to deal with the simple problem of how to dispose of his wages. Parliament did not intend to treat as cured a man whose optimum prospect of recovery was to be fit for that sort of half-life; the wife had, therefore, proved that the husband was incurably of unsound mind and was entitled to a decree nisi.

WHYSALL *v.* WHYSALL, *Probate, Divorce and Admiralty Division (Phillimore J.)*: July 31, 1959. R. J. A. Temple, Q.C., and M. Heald (P. Alec Cook, The Law Society, Nottingham); Roger Ormrod, Q.C., and K. R. Bagnall (The Official Solicitor).

E. JONES,
Barrister-at-Law.

Our Legal Correspondent writes:

Insanity was first introduced as a ground for divorce in 1937, when it was provided that either party to a marriage might petition for divorce on the ground that the respondent was incurably of unsound mind and had been continuously under care and attention for a period of five years immediately preceding the presentation of the petition. The 1937 Act carefully defined the circumstances in which the respondent should be deemed to be under care and attention, but attempted no definition of the phrase "incurably of unsound mind".

This state of things was preserved when the divorce law was consolidated by the Matrimonial Causes Act, 1950. The Divorce (Insanity and Desertion) Act, 1958, extended the list of circumstances in which the respondent is deemed to be under care and treatment, but still did not give any definition of "incurably of unsound mind".

The lack of a definition was not on the whole a problem before 1958. The respondent was deemed to be under care and treatment only if detained (itself evidence of insanity) or if admitted as a voluntary patient under the Mental Treatment Act, 1930. The real question for the Court was therefore whether the condition could be said, in the light of medical knowledge at the time, to be incurable.

The 1958 Mental Health Act has removed the emphasis on detention. The five-year rule remains, but a patient is now deemed to be under care and attention if receiving "treatment for mental illness" in an ordinary hospital. This fact, coupled with the advances in medical knowledge, make it more urgent to find at least a working definition of the degree of mental illness which will justify a divorce. Mr. Justice Phillimore's judgment is of considerable importance in this connection. His Lordship applied the test, whether the patient was likely ever in the future to be able to manage his own affairs and live a normal married life, which in practice is probably the most satisfactory test.

Income Tax of Part-time Consultants

Expenses incurred in treating patients under the National Health Service Act, 1946, by part-time specialists who also have private patients have to be deducted under schedule E of the Income Tax Act, 1952, and not under schedule D. Because of the difference in wording of the rules for assessment of tax, outgoings which might be deductible under schedule D (dealing with profits or gains arising from any "profession, employment, or vocation") might not be deductible under schedule E (profits or gains arising from an "office" or "employment"). The Special Commissioners of Income Tax had

held that five consultants were taxable under schedule D and the inspectors of taxes concerned appealed.

Mr. Justice UPJOHN, giving judgment, said that the question for determination was whether profits or gains from appointments held under regional hospital boards arose from an " office " or " employment " within schedule E.

Since 1946 a specialist who wished to serve under the National Health Service must take a whole-time or part-time appointment with, and become a member of the staff of, a board; the large majority of specialists took part-time appointments. It followed from the nature of the professional status of a specialist that his work was subject to no control or direction as to how he should carry it out; that appeared to be so even for those on the lowest rung of the professional ladder. The law now was that all offices and employments for profit, whether public or private, fell within schedule E. A specialist, in carrying out his part-time appointment with a board, was not merely rendering services as a private, though professionally skilled and qualified, individual, but was the instrument of the Minister to carry out part of the national scheme " to provide for the establishment of a comprehensive health service for England and Wales ". He was thus carrying out necessarily a public function, and was properly described as the holder of a public office.

So far, his Lordship agreed with the Commissioners. But they had decided that nevertheless the consultants were assessable under schedule D on the ground that the hospital appointments were a necessary incident of their professions. That argument ought not to succeed. Once the conclusion was reached that the National Health Service appointment was the holding of an office, the expenses attendant thereon must be deducted under the rules applicable to schedule E, and under no other schedule. Expenses incurred by the specialists in domiciliary visits and as *locum tenens* must be similarly treated.

MITCHELL AND EDON (H.M. INSPECTORS OF TAXES) *v.* ROSS—*Chancery Division* (Upjohn, *J.*): July 21, 1959. Counsel and solicitors: R. O. Wilberforce, Q.C., E. B. Stamp, and A. S. Orr (Solicitor of Inland Revenue); F. Heyworth Talbot, Q.C., and J. L. Creese (Hempsons).

MARGARET G. THOMAS
Barrister-at-Law.

Our Legal Correspondent writes:

Both the Special Commissioners and Mr. Justice Upjohn held that the consultants were holders of a public office. This part of the decision is not surprising: the term " public office " has always been interpreted in a very wide sense. It has been held, for instance, to cover a director of a private company, the public status deriving from the fact that a private company is registered under the Companies Acts.

But his Lordship refused to follow the Special Commissioner's finding that the hospital appointments were a necessary part of the consultants' profession. He therefore held that the consultants were taxable under schedule E. The practical consequence of this will be that in future part-time consultants will be less generously treated in the matter of expenses. In particular, it is unlikely that they will be allowed to deduct the expense of travelling to and from hospital. Thus, a practising solicitor who held the part-time appointment of clerk to the justices in another town was held not to be entitled to the expense of travelling there. A similar claim from a London barrister who held the office of recorder of Portsmouth was also disallowed.

It is worth emphasising that Mr. Justice Upjohn's decision casts no reflection on the professional status of doctors holding hospital appointments. On the contrary, his Lordship said that the work of a specialist was under no control or direction as how he should carry it out.

The decision is probably correct as the law now stands, but there is surely a case for amending the law. It may not be " necessary " for doctors to take up hospital appointments, as the Special Commissioners suggested, but the doctor who accepts such an appointment is in fact carrying on his profession. In effect, part of his fees are paid by the State and that part of his fees ought not to be treated differently for tax purposes.

In England Now

A Running Commentary by Peripatetic Correspondents

HEALTH-WISE, our archæological expedition was well equipped. When we set off for a Scottish island we had with us two doctors. As one was a general practitioner and the other a psychiatrist, body and mind were both catered for. We also had among our members a pharmacist, a physiotherapist, a path. lab. technician, and, to help us with any discoveries of medical importance, a girl from the M.R.C. The general practitioner had a varied collection of drugs ranging from aspirin to ergometrine. The pharmacist contributed numerous empty drug tins. The physiotherapist brought some nylon rope. (We never knew what this was intended for but it came in very handy as a clothes-line.) The lab. technician came equipped with slides and test-tubes. We hoped to use these for pollen analysis but were prepared to do a bit of parasitology if necessary. The psychiatrist didn't believe in drugs but expressed willingness to hypnotise anyone who needed an operation.

Unfortunately the party remained very healthy. The G.P. offered to keep himself available at surgery hours, but no-one came. The psychiatrist looked vainly for group neurosis and suggested interpretations of dreams at breakfast. When the lab. technician hurt his foot he did not consult the physiotherapist; she was his wife, so doubtless he had his reasons.

Gradually our professional functions faded into the background as we all became archæologists. Like agitated hornets we buzzed about the island on an assortment of scooters and motor-bikes; and it was this mode of transport which led to the only medical emergency. After a couple of cold wet days the psychiatrist noticed puzzling red itchy areas on both hands. Medical and lay opinion was sought and the diagnosis was unanimous. In the middle of one of the best summers for years, I had developed chilblains.

* * *

During my stay in hospital I was engaged in the usual battle of wits with the hospital staff to find out what was really wrong with me and what they were going to do about it. The nurses were very ready to talk but knew nothing to the point. The ward sisters gave an impression of omniscience, but their guesses were often unfounded. The consultants were past masters of reticence; the registrars were always too busy; the housemen were sometimes more forthcoming if you could catch them at a slack moment. But the really helpful people were the medical students. Get a keen student interested in your case and he will tell you everything. One that was specially attached to me was the first to break the news that I was going to have an operation; next day I got a preliminary warning from the houseman, but it was not till the day after that I got it officially from the surgeon.

* * *

David aged 12 went on a school bus trip to the seaside. It was an intermittently sunny day, but not really very hot and it rained on and off after 6 P.M. David had a good time and seemed all right when he arrived home, and he ate a good supper. But later his mother wondered if he had " heat stroke ", for after she and her husband went to bed they heard David get up and found him at the window. He said a man had tried to get in and that fishermen were pulling in his line and stealing his lobsters. After that he didn't sleep at all, but caught lobsters all night and wrapped them in his blankets. Next morning he said the Indians had come to kill his little brother Roy, and Paul his friend next door. He shrieked and burst into tears saying his brother was dead. When his father came home he was quieter because he said he wore a revolver and could ward off the Indians. (David's father carries a steel ruler in his overalls). After this David quickly became normal.

The story really began with David's mother's anxiety about his travel sickness. She bought him a tube of tablets for this and he finished the lot on the return journey.

Letters to the Editor

DIMINISHED RESPONSIBILITY

SIR,—If, as Dr. Maddison suggests in his article last week, criminologists and lawyers are justified in feelings of uncertainty about the contribution of psychology and psychiatry to such studies, how much more justified would be doubts on the part of those trained in philosophy or semantics after a careful reading of it.

The issue of free-will versus determinism is of crucial importance in psychiatry and criminology, but a study of the history of the problem shows that it does not yield to any such facile or clear-cut solution as Dr. Maddison would have us believe.

It may well be that, in the past, rationality has held an exaggerated place in Western thought. But that is no reason for throwing it overboard altogether. Because the ego does not hold undisputed sway over the psychic economy we do not, for that reason, abandon it.

When material from the unconscious presents itself to the conscious mind, whether in the form of dreams, fantasies, or symptoms, there does not seem to be an inevitable process whereby such phenomena are transformed into motor activity. Rather is consciousness presented with a choice, as to what to do with these impulses, thoughts, and images. It can entertain them, reject them, act them out, or work on them; but there is a continual problem of choice, which goes to make analytical work something fit for human beings to do, and not simply a mutual observation by two beings whose every act is determined.

That, to my mind, is what analysis and psychiatry are about, and this is what gives them relevance to problems of human behaviour, which includes the field of criminology.

London, S.W.5. W. H. ALLCHIN.

SIR,—I should like to support wholeheartedly all the opinions expressed by Dr. Maddison. I hope very much that leading psychiatrists in this country will be able to awaken public opinion to the implications of the fact that free-will is an illusion so that the way may be paved for the reform of our legal system which, at the moment, rests on false premises.

I am thinking of compiling a scrapbook of some of the moralistic and foolish exhortations given by learned recorders and judges to fellow human beings in the dock.

The Towers Hospital, Humberstone, Leicester. H. B. KIDD.

THE MEDICAL SUPERINTENDENT

SIR,—The members of the Group Medical Committee (Nottingham no. 3 area) view with concern recent developments which tend to weaken the position of the medical superintendent of psychiatric hospitals and wish to affirm their conviction that most of the modern advances in psychiatry, especially in the field of "administrative psychiatry", would not have taken place without the specific role of individual superintendents and that a weakening or disappearance of their function would lead to an irreparable loss of the advances made.

We are of the opinion that many of the tendencies to undermine the position of the superintendent are based on the common but mistaken idea that a psychiatric hospital is basically "just like any other hospital", and that psychiatry is "just like any other branch of medicine". We feel that such facile analogies and generalisations obscure the true picture and that future mental-health policy must be based on a correct assessment of the part which psychiatric hospitals will have to play. Whilst many other hospitals can and do function well under a lay administrator or some medical committee this is not possible in the case of psychiatric hospitals. We should like to mention the following points, which in our opinion indicate the need for the continuation of the office of medical superintendency. These points can be grouped progressively under three headings: (1) in the psychiatric hospital, (2) in the mental health service, and (3) in the relationship to the community.

(1) A general hospital may have a great number of departments which may well function independently of each other. A psychiatric hospital on the other hand is (or, at any rate, should be) an organic structure; it is a therapeutic community —i.e., a super-departmental organisation which depends essentially on a central policy represented by the medical superintendent. It is not only the coordination of the various departments that is the main responsibility of the superintendent, but the creation of that higher organisation. Such questions as the establishment of workshops, hostels, clubs, outpatient clinics of various types, day hospitals, and many others require medical planning. We have no doubt that this cannot possibly be carried out by a lay administrator, individual consultants or a medical committee.

(2) The psychiatric hospital, however, represents only one aspect of a mental health service, which in its ideal form should be comprehensive. It is being recognised that a great deal of responsibility for psychiatric care rests with the community, and the forthcoming mental health legislation is paying due regard to this aspect. Inevitably, local authorities will have to develop their pre-hospital and post-hospital services to a larger extent than they have done in most cases so far. The unfortunate division of responsibility for the patient between hospital and local-authority services can be overcome only if full use is made of "joint user" arrangements under which the medical superintendent acts in an advisory and coordinating capacity for the local authority. His role then becomes comparable with and complementary to that of the M.O.H.

(3) A full, comprehensive mental health service, such as is envisaged by this committee, forms part of the general community services. Provision must be made for psychiatric advice to child guidance centres, marriage guidance clinics, the Courts, the probation service, the welfare services, the Ministry of Labour, the Ministry of Pensions, and other social agencies. All this requires a central policy to coordinate the different services and reconcile conflicting demands. Planning for future needs, the initiation of action and the assumption of leadership are the functions of the medical administrator representing the mental health service, and only the medical superintendent can speak with the necessary authority. He represents the psychiatric hospital to the community and in return makes possible in the hospital the fulfilment of the community's needs. His work is to harmonise and balance the interaction of hospital and community and he can only do this if he is able to stand above divisions in the hospital and sectional interest in the community. It is difficult to see how this can be done by a lay administrator or any committee.

For these reasons this Group Medical Committee, which consists of eight consultants (including three superintendents) and four S.H.M.O.s of three hospitals, would welcome an exchange of views with others who find themselves in agreement with us in order to consider what steps could be taken to prevent a weakening of the position of the medical superintendent. It is perhaps not unnecessary to say that this letter was first suggested and drafted by members who are not medical superintendents. We realise that medical superintendents themselves might

hesitate to take any action because they could be suspected of speaking " pro domo ".

Comments are invited and should be sent to the Honorary Secretary, Nottingham No. 3 Group Medical Committee, Mapperley Hospital, Nottingham.

Mapperley Hospital, Nottingham. H. FISHER Hon. Secretary.

SIR,—I read with interest the complaint by " Consultant Psychiatrist " (Aug. 15) that his medical superintendent discharges his patients without his knowledge. In mental-deficiency hospitals this is almost the usual practice. Admissions, transfers, parole, &c., are frequently arranged by the medical superintendent without reference to his medical staff, and once I even found that an empty ward of mine had been filled overnight without my knowledge!

Much light has been shone into the dark places of general psychiatry in recent years, but mental deficiency still has many murky corners that require the enthusiastic application of new brooms. For example, there is often a persistent refusal to divide patients between the senior medical staff, so that " clinical responsibility " can be given some meaning. This probably springs from experiencing the pleasures of administrative office routine over a long period, during which any clinical skills have atrophied.

Medical staffs in mental-deficiency hospitals are often so small that medical staff advisory committees cannot be effectively formed; but, now that legally there is no differentiation between mental and mental-deficiency hospitals it is to be hoped that a similar more enlightened approach will be generally applied.

ANOTHER CONSULTANT PSYCHIATRIST.

BENACTYZINE IN ANXIETY STATES

SIR,—The recent spate of new drugs, especially in the field of psychiatry, has led to numerous clinical trials, many of which are never formally published because of a negative or equivocal result. This is for obvious reasons a matter of regret. Some therapeutic trials require the most detailed reporting but there are many where a brief outline of the method and results should suffice. We suggest the following letter may serve as an example of how such reports could be speedily published without requiring much of your precious space. The trial reported concerns *benactyzine* in the treatment of anxiety states.

Conflicting and inconclusive results with this drug in anxiety states are reported by Hargreaves et al.[1] and Hamilton.[2] The design was the double-blind method with random allocation to test and control groups. The patients were treated as outpatients with a standard dose of 1–2 mg. t.d.s., the larger dose being given to patients of heavier bodily build. Controls received an inert placebo. The essential criteria for selection were symptoms of anxiety and/or tension predominating in the clinical picture. The trial period was three weeks, patients being seen each week by the same observer who interviewed them at the initial interview. A prognosis rating was made before the treatment. At the weekly follow-up interview patients were rated into 6 operationally defined groups and detailed notes of other features, such as side-effects, made.

Of 52 patients in the investigations 18 were excluded from the final analysis, either because they failed to take the tablets as directed or were otherwise uncooperative. Of the 18 who failed to cooperate 7 (3 on the drug and 4 controls) lapsed in attendance. 11 (9 on drug and 2 controls) discontinued taking the tablets because of side-effects. The main side-effects complained of were: dizziness (2), digestive upset (3), trembling sensation (3), headaches (2), and faintness (2). The patients in the control group who discontinued complained of dizziness. Of the remainder, 15 patients were in the test and 19 in the control group. The two groups were comparable in most important aspects, such as age, sex, symptom distribution, mode of onset, and previous psychiatric treatment. Prognosis ratings before treatment showed very similar distribution in both groups. There was no good reason to suppose any significant difference between the groups that may have influenced the response to the drug.

The changes each week showed no definite difference between the test and control groups over the three-week period of treatment. Patients receiving benactyzine did show a slightly greater degree of improvement than those who did not, but the difference might be accounted for by any drug with a slight sedative effect. The difference between the test and control group were a little more marked at the extremities of the rating scale. Nothing was found which would differentiate those few patients who appeared to derive marked benefit from benactyzine from those in the control group who obtained almost equivalent relief from inert tablets.

To sum up: a double-blind control trial of benactyzine in 52 outpatients suffering from anxiety states showed that in a dose of 1–2 mg. t.d.s. for three weeks, this drug had little, if any, value in the symptomatic treatment of their condition. The apparent slight benefit after benactyzine, when compared with an inert placebo, was offset by the much higher incidence of side-effects.

Workers interested in more details of method and results can obtain these from the authors.

Uffculme Clinic, Moseley, Birmingham. J. A. HARRINGTON W. MAYER-GROSS.

1. Hargreaves, G. R., Hamilton, M., Roberts, J. M. *J. ment. Sci.* 1958, **104**, 1056.
2. Hamilton, M. *ibid.* p. 1062.

FAMILIAL HEREDITARY ANGIO-ŒDEMA TREATED WITH PROMETHAZINE

SIR,—Halpern [1] first reported successful therapy of allergic angio-œdema with promethazine (' Phenergan '). Familial hereditary angio-œdema has not been treated previously, we believe, with promethazine.

Familial hereditary angio-œdema is a rare disease of unknown ætiology characterised by: inheritance as a mendelian dominant trait [2]; recurrent attacks of acute circumscribed non-inflammatory œdema involving the skin, subcutaneous tissue, and muscle, and/or the mucosa of the pharynx, larynx, or gastrointestinal tract; a high mortality from laryngeal œdema.[3] No treatment previously described, other than permanent tracheotomy,[4] has been effective in preventing death from laryngeal œdema.

Our patient is a 32-year-old Caucasian female affected by this disease since the age of 2. Her father and paternal grandfather both died of this disease from acute laryngeal œdema. She had been treated over the previous 8 years with intermittent diphenhydramine hydrochloride ('Benadryl'), 75 mg. intramuscularly, for acute attacks of pharyngeal or laryngeal œdema, or attacks of intestinal obstruction, with the aborting of severe progression of attacks. There is a report in the literature, however, of death from acute laryngeal œdema, despite large doses of diphenhydramine hydrochloride, intravenously.[5] The possibility of permanent tracheotomy was discussed with the patient, but she refused to consider it.

During the past 12 months the patient has been treated with oral promethazine (25 mg. t.i.d., p.c., and 125 mg. h.s.), with 5 mg. of metamphetamine in the morning. The large nocturnal dose of promethazine is well tolerated by the patient, and this probably exerts its non-specific capillary permeability blocking effects throughout the following day.[1] Although the frequency

1. Halpern, B. N. *Bull. N.Y. Acad. Med.* 1949, **25**, 323.
2. Phillips, J. M., Barrows, W. M. *Genetics*, 1922, **7**, 573.
3. Bulloch, W. *Inh. Eugen. Lab. Mem.* 1909, **9**, 38.
4. Apert, E., Delille, A. *Bull. Soc. méd. Hôp. Paris.* 1904, **21**, 1022.
5. Sheldon, J. M., Schreiber, E. O., Lovell, R. G. *J. Lab. clin. Med.* 1949, **34**, 524.

of attacks has not diminished, occurring approximately once every two weeks, the severity of œdema is much less, and she is able to abort severe progression of swelling by taking additional promethazine—100 to 200 mg. orally, or 50 to 100 mg. intramuscularly. The patient was not maintained on a larger daytime dose of promethazine because of involuntary facial movements that occurred on 50 mg. t.i.d., p.c., or with a total daily dose of 300–400 mg. The patient's two children, both of whom show evidence of the disease, also have responded to promethazine therapy.

Because promethazine treatment has been effective so far in preventing severe attacks of swelling in our patient, we believe other patients with familial hereditary angio-œdema should be considered for a trial with this drug.

N. S. LANDERMAN
Walter Reed Army Hospital and H. E. RATCLIFFE
Walter Reed Army Institute of Research, E. L. BECKER.
Washington, D.C.

RESOURCES FOR RESEARCH

SIR,—One of the tragedies of, at any rate, our medical time, is that few people, especially those under 45, have time to have ideas. Very often really major advances are not made by high-powered teams using complicated apparatus in large research units: they are the result of intuitive thinking by people with time to reflect.

In more spacious days appointment to a major hospital meant an assured standard of living and time to think. Now it is a question of maximum sessions, domiciliary visits, and endless consultations and committees. In those days too, juniors, although unmarried and penniless, had fewer routine duties and were taught to reflect rather than to pass examinations. Nowadays "think-time" is to most people non-existent.

It seems to me that the question of research, progress, and contributions made by practising doctors is not so much a matter of jobs and facilities, but one of reorganisation so that there is time to think, reflect, and produce papers that are more than reviews of cases and literature.

"What is this life if, full of care,
We have no time to stand and stare?"

Medical Research Unit,
Institute of Directors,
London, S.W.1. H. BERIC WRIGHT.

LACTATION AND FEAR

SIR,—Some of Dr. Brian Stanford's sequence of thought has clinical confirmation, for apprehension about feeding certainly makes many mothers sweat freely; but it would be hard to tell whether the secretion differs qualitatively from that of others. I would, however, differ from Dr. Stanford when he says "Mothers who for psychological reason, or because of painful nipples, are frightened of suckling, have difficulty in persuading the baby to take"; and he suggests that fear-sweat or a similar process affecting the milk as it is secreted may make the milk distasteful. As I see it, if a breast does not offer a good enough hold, the mother's, the baby's, and the midwife's resulting awkwardness often causes the baby's upper lip to occlude the nostrils while the breast gives the baby no satisfaction when he goes to feed. The baby has only to experience this a few times for him to cry before even giving a feed a chance. This situation can be made worse where the mother moves away because she dreads feeding but even if she did not dread it before she will certainly soon do so, for I consider being cried at and rejected like this is the greatest inducement of sweating and reluctance to feed in a mother. And the same poorly protractile nipple is the kind which easily goes sore. I believe therefore that usually it is the rejecting baby which makes the mother sweat rather than the other way round and that prevention lies in the antenatal use of shells, not in perfumes or smokes.

University College Hospital,
London, W.C.1. MAVIS GUNTHER.

BREAST CANCER

SIR,—Sir Robert Platt (June 20) has referred to one of the fallacies arising when breast cancer is treated on statistical rather than pathological principles. There are others.

The work of Halsted,[1] Handley,[2] and others, put the surgical treatment of breast cancer on a sound scientific basis. Certainly most of us thought so—until McWhirter[3] advocated a form of treatment which entirely disregards Halsted and Handley's principles. The "proof" that these should be disregarded is statistical. This, to me at least, is the dullest and most unreliable way of establishing biological facts. Statistics certainly have had their successes, but in general they should be used to give us a sense of proportion, and to show if our individual work is up to standard.

One of the worst fallacies of the statistical method is the assumption that every surgeon does an equally skilled radical mastectomy. With experience the surgical pathologist can name the surgeon by looking at the operation specimen.

A short time ago the Derby radiotherapist, Mr. A. G. G. Melville, told me he was going to work out our survival-rate for cancer of the breast, for comparison with other series. Knowing the surgical habits of the various surgeons, we decided it would be of interest to see how the others compared with one who always did a full radical operation and did not pass cases on for treatment by changing members of the house staff. This surgeon had just over 80% five-year survivals in patients not shown to have metastases in the axillary lymph-nodes; the next best was only a little over 50%. The "next best" was not one man but many; so we did not learn if the other surgeons who regularly did a full operation compared favourably with the man whose series was simple to analyse.

This investigation by Mr. Melville brought me out of the fog into which I, like many others, had been thrown by McWhirter.

Haagensen [4] lays down definite criteria for operability in breast cancer. He aims at perfection in all his work. He says that a case is either operable or inoperable. If the former, the operation should be so thorough that there is no point in following it with radiotherapy. Neither pre- nor post-operative radiotherapy is given at the Massachusetts General Hospital, Mayo Clinic, or Presbyterian Hospital, because no advantage has been found in it if the operation is scientifically planned. If the case is inoperable it should be treated by radiotherapy alone.

Twelve years ago I saw with Haagensen a patient who, after radiotherapy, appeared to me to be operable. I asked him why he would not operate on her. There were two reasons: (1) an inoperable case never becomes operable as a result of other treatment, and (2) if he operated on cases like that the radiotherapists would never learn that they cannot cure the condition. With his introduction of the "triple biopsy", Haagensen sought to raise the accuracy of the selection of the operable cases from about 82% to 100%. While I am second to none in my admiration of Haagensen and his work, I do think he has gone too far in this search for precision.

1. Halsted, W. S. *Trans. Amer. surg. Ass.* 1907, **30**, 287 (also papers of 1890–91, 1894–95, 1898, and 1912 quoted by Haagensen).
2. Handley, W. S. Cancer of the Breast and its Treatment. London, 1922.
3. McWhirter, R. *Brit. J. Radiol.* 1955, **28**, 128.
4. Haagensen, C. D. Diseases of the Breast. Philadelphia and London, 1956.

Treatment should not be based either on statistics or theories but on observed pathological processes. In cancer work generally we know the prognosis of the group but not always of the individual to be treated. We should aim at 100% accuracy but hardly expect to attain it. I would think the figure Dr. E. C. Atkinson (June 20) asks for (what proportion have an inherent tendency to grow and metastasise rapidly) is just under 18%—small enough to be ignored in planning treatment for the average case.

When we examine the specimen resulting from a radical mastectomy we not infrequently see permeation of the pectoral lymphatics, over and in the pectoralis major muscle. Treatment by local mastectomy must therefore be expected to leave cancer locally, and radiotherapy is relied on to " cure " this. I would be interested to learn from surgeons who have this confidence in radiotherapy why they are not more conservative still? Why operate at all? There can be only one answer—that the primary growth is more radioresistant than its extensions. Do we know that? If it is true, why remove the breast instead of just the tumour? Surgeons used to tell me that if the breast must be removed it makes little difference to the woman whether the operation is local or radical. Some appear to have abandoned this view.

In the days when the Derby surgeons all did a full radical operation I rarely saw recurrence in the scar. Most of those I did see had been operated on elsewhere. Now I see it quite often in our own cases. This problem has been studied fully by Hugh Auchincloss Jr.[5] who has completed the work of his father. The causes of local recurrence are:

1. Persistence (rather than recurrence) due to inadequate local removal of skin. This is shown to be much less important than was believed.

2. Retrograde spread from intercostal and internal mammary lymphatics affected at the time of the operation.

3. Inadequate care by the surgeon to prevent cancer cells being spilled into the operation wound.

4. Inadequate axillary dissection. This may include operating on inoperable cases.

Causes 3 and 4 can be avoided by careful surgical technique and the proper selection of cases for operation. Cause 3 will operate as a rule in patients treated by local mastectomy and radiotherapy: absolute reliance is here placed on irradiation, and from the greater frequency with which I now see local recurrence I judge that this reliance is misplaced. Cause 2 is very difficult to control and it accounted for most of the 14·5% local recurrences noted by Auchincloss, the tumours in this group tend to be beneath the aerola or medial to the nipple.

We can state criteria by which individual surgeons should judge their own work.

1. The five-year survival-rate for patients without demonstrable metastases in the axillary lymph-nodes should slightly exceed 80%.

2. The five-year survival-rate for such patients operated on by a junior of the surgeon in charge should equal his own.

3. Local recurrence in the operation site should not occur except in some of the cancers in the areolar region, medial to the nipple, or with axillary metastases.

4. No time should be lost because of difficulty in diagnosis.

5. There should be no cases with radical treatment for benign conditions.

The last two criteria call for the use of frozen section at the time of operation, quite often. This service should be freely available wherever breast lesions are operated on.

5. Auchincloss, H., Jr. *Cancer*, 1958, ii, 611.

In January, 1853, Francis Donaldson,[6] discussing the importance of the microscope in the correct management of breast lesions, wrote:

" We unhesitatingly say that often there is great confusion and doubt even among distinguished surgeons, at the most important period of the disease."

The confusion now must be greater than then. If surgeons would become scientists again instead of statisticians, the problems could be resolved. Haagensen sets out the scientific aspects of diagnosis and treatment very clearly.

Derbyshire Royal Infirmary, Derby. G. R. OSBORN.

AN EXAMINATION PAPER FOR . . . ?

SIR,—It is naïve to suppose that, by looking at an examination paper, any idea of the standard expected can be obtained; indeed, in most qualifying examinations it is the candidates themselves who set the standard.

Part of the onus of the training of nurses falls upon the medical profession, and rightly the General Nursing Council has medically qualified examiners on its panel. But an interesting question emerges from the letter of your correspondents last week—what does the doctor expect of the qualified nurse?

Is the nurse supposed to carry out the doctor's instructions blindly and unintelligently, between moments of smoothing the patients' pillows, or is she supposed to administer the treatment he orders with interest, sympathy, and understanding?

The General Nursing Council for England and Wales is fully aware of the need for good, practical, bedside nurses, unburdened with a great deal of theoretical knowledge and provides a perfectly adequate two-year training for this purpose. But the G.N.C. is also aware that responsible ward sisters, tutors, and matrons are needed not only for this country but for the Colonies; the public-health services are also crying out for recruits who need the basic training of state registration. Candidates for such posts must be intelligent, responsible women who are aware of the problems of modern medical treatment.

We need far more nurses with a two-year, practical training for the Roll of the General Nursing Council and we need fewer nurses training for State Registration. The nursing profession was greatly helped in the 'thirties by *The Lancet* commission; we continue to need the help of our medical colleagues today in an understanding of some of the far-from-simple problems that confront us.

ONE OF THE HANDMAIDENS.

SIR,—I was interested to read the letter of Aug. 15 from Dr. Walther and Dr. Raeburn of Whipps Cross Hospital, condemning the questions set in the last Final State Examination for the General Part of the Register in the Principles of Medicine and Nursing as more suitable for a Membership paper, final M.B., or Conjoint Medicine.

Dr. Walther and Dr. Raeburn emphasise their view that the questions set assume a knowledge far in advance of that necessary for a State Registered Nurse to carry out her nursing care, and in consequence frighten the candidates for examination.

It may interest your readers to know that no adverse criticism of the paper in question has been received from any member of this Association, while, on the contrary,

6. Donaldson, F. *Amer. J. med. Sci.* January, 1853, p. 49.

many student nurses in various types of training schools agree in their opinion that this particular paper was both fair and reasonable.

Student Nurses Association,
The Royal College of Nursing,
London, W.1. I. E. SPALDING.

SIR,—I wonder whether Dr. Walther and Dr. Raeburn have studied the present syllabus for the training of those who desire to become State Registered Nurses. As I see it the present tendency is to raise the initial educational standard for nurse training and to increase the academic knowledge necessary to pass the final examinations. It is strongly held in some quarters that by so doing the brightest of the "school leavers" from our grammar schools will be attracted to nursing in greater numbers. We certainly want as many of these as we can get although it should be remembered that even if all the grammar-school grade "leavers" went in for nurse training we would still be short of nursing staff. What we do want so badly at the present time are "two years trained practical basic nurses" to fill the vacant places. The present assistant nurses training course is well constructed to do this if full status of "nurse" was assured and advancement to higher grades of nursing made possible at the end of the two years. As the law stands at present this is impossible.

Leeds. C. W. VINING.

PATHOGENESIS AND TREATMENT OF ENDOCRINE EXOPHTHALMOS

SIR,—Sir Russell Brain (Jan. 17) and other authors have emphasised that an increase in the content of thyrotrophin in body fluids is not necessarily found in patients with exophthalmos. Even if the evolutionary phase of the exophthalmos has passed and hyperpituitarism is no longer present, residual exophthalmos may be perpetuated by permanent anatomical changes—e.g., retroorbital œdema, infiltration, or fibrosis.

Residual exophthalmos may have arisen either from euthyroid exophthalmos, or from Graves' disease[1]; in both cases the level of body-fluid thyrotrophin is normal or subnormal, as the hormone is no longer being produced in excess. It is an error to speak of the condition which arises after thyroidectomy as *residual* exophthalmos, because this has been precipitated by the freeing of the pituitary from the influence of thyroxine.[2]

From the clinical point of view it is essential to distinguish between evolutionary and residual exophthalmos, because treatment by inhibition of the pituitary (thyroxine, œstrogens, or radiotherapy) is indicated in the evolutionary form only. In the residual form local treatment with hydrocortisone, or radiotherapy to the orbit, is the only therapy of value.

CFR (no. 1) Hospital,
Bucharest, Rumania. EMANUEL I. COHEN.

NAMES FOR DRUGS

SIR,—The paper by Mr. Boura and others (July 11) is interesting not only because the contents of the paper are interesting but also because of the names given to the compound used. The third and last, or what we might call the cognomen, being bretylium tosylate.

I am sure all practising physicians will agree that there are already far too many names for drugs—official and proprietary—and that this makes for considerable difficulties. We can be quite sure that this latest compound will be marketed under different names by different firms; but this is to be expected, not only from long-established custom but also because the existing name is meaningless. If it suggests anything it is an organic salt of some (probably poisonous) metal, such as beryllium.

Surely the time has come for a chemical compound which is to be made available for therapeutic purposes to be given a registration number comparable with that of a mechanically propelled vehicle. Even now there are more cars than drugs, but each car can be instantly distinguished from every other. In the same way that the county of a car's registration can be identified, a suitable registration for a drug could convey the more important data concerning it, with no more possibility of confusion than would arise from illegible writing—a hazard that already exists.

Edgbaston, Birmingham. W. M. PHILIP.

TRIAMCINOLONE IN CHRONIC PSORIASIS

SIR,—The use of triamcinolone in psoriasis was described by Shelley et al.,[1] who investigated its effects in sixty cases of all types. They gave doses averaging 12–16 mg. daily by mouth, the limits varying from 4 to 32 mg. A rapid and definite response was noted in thirty-six (60%), and the psoriasis cleared in some patients within 2–4 weeks, but recurrence regularly followed withdrawal of the steroid. In view of these interesting results, I decided to try triamcinolone in a series of very chronic cases.

Sixteen patients suffering from psoriasis of 3–50 years' duration were contacted. None of these subjects, to his or her own knowledge, had ever been clear of scaling and the typical salmon-red erythema. Since treatment was carried out during the last 3 months of the year, when psoriasis is usually at its worst, it was thought that any good results from treatment would be more significant.

Triamcinolone in the form of 'Adcortyl' tablets, 4 mg. or 1 mg., was used in this investigation. Although all the cases were chronic they naturally varied in severity, but it was decided to use the same initial adult dosage of 12 mg. daily, and to reduce this dose gradually so as to complete the course in 7–8 weeks (12 mg. was given for 3–4 weeks, 8 mg. for 2–3 weeks, and 4 mg. in the final stage. These doses were halved for a child aged 9). Even if clearance was noted during treatment, the course was still completed, as I hoped that an adequate period of treatment and a gradual reduction of dosage would produce a better clearance-rate and longer freedom from recurrence when treatment was stopped. No other drug was used internally or externally during this trial.

The results achieved are shown in the table. If one excludes case C, where treatment could not be completed because of

1. Shelley, W. B., Harun, J. S., Pillsbury, D. M. *J. Amer. med. Ass.* 1958, **167**, 959.

EFFECTS OF TRIAMCINOLONE IN SIXTEEN CASES OF PSORIASIS

Patient	Sex	Age (yr.)	Duration (yr.)	Clearance in weeks after commencement	Recurrence in weeks after end of course	Remarks
A	F	21	10	4½	4	..
B	F	34	20	4	5	..
C	F	75	50	..	..	Course not completed because of unrelated intercurrent illness
D	F	55	50	6½	3	..
E	F	61	18	7	6	..
F	F	9	3	6	1	..
G	M	42	11	7	6½	..
H	F	36	10	7	6	..
J	F	44	9	7	5	..
K	F	56	12	4	1	..
L	F	21	8	4	10	..
M	M	47	14	4	10	..
N	M	44	12	..	..	Improved but did not clear
O	F	61	6	4	..	Still clear after 22 weeks
P	M	47	20	5	12	..
Q	M	42	7	3	..	Still clear after 22 weeks

1. Cohen, E. I. *J. clin. Endocrin.* 1956, **16**, 559.
2. Cohen, E. I. *Pr. méd.* 1958, **46**, 1040.

intercurrent illness, 93% were cleared within 3–7 weeks of commencing treatment with triamcinolone. Only two patients developed side-effects of a very minor nature, and these disappeared quickly after the completion of the course.

Taking into account the chronicity of the cases under investigation, the period of freedom from recurrence does not create a despondent outlook; five patients (33%) were still clear 10 weeks after completing the course of treatment. Itching, which was the predominant symptom in all cases, was relieved within 7 days.

In dealing with a skin condition whose ætiology is so complex, it is difficult to visualise any single drug as the complete treatment. Triamcinolone is not claimed to be a cure, but, without being too optimistic, the results of this trial indicate that it has a place in treatment, especially in the alleviation of the disease.

I wish to thank Dr. F. F. Hellier, physician in charge of the dermatological department, Leeds General Infirmary, for his helpful comments; to E. R. Squibb & Sons Ltd. for supplying the triamcinolone tablets; and to Mr. W. W. Heseltine, Regional Research Director for his kindness and help.

Leicester. ERIC LODGE.

CORTICOTROPHIN AND ADRENAL CORTICOIDS IN PRE-ECLAMPTIC TOXÆMIA

SIR,—F. J. Browne [1] advanced the theory that pre-eclamptic toxæmia and eclampsia are due to over-production of adrenal cortical hormones and corticotrophin, brought about by a dysfunction of the placenta, which in normal pregnancy destroys any excess of adrenal corticoids.

Having at our disposal three routine methods for the assay of corticotrophin in blood,[2] and 17-ketosteroids [3] and 17-hydroxycorticoids [4] in urine, we studied these hormones in 55 normal pregnancies and in 12 women with pre-eclamptic toxæmia.

In normal pregnancies, corticotrophin is increased because it is produced by the placenta,[5–7] the 17-hydroxycorticoids are likewise increased,[4 8 9] and the 17-ketosteroids are mostly normal, with unexplained rises in rare cases only.[4]

With regard to corticotrophin, earlier examinations had shown that its increase in the blood of pregnant women is irregular, without any apparent reason.[10 11] We have re-examined the problem, bearing in mind the possibility that women showing increased corticotrophin levels might have pre-eclamptic toxæmia. This has, however, not been borne out by our studies.

In 55 pregnant women examined at term, only 11 (20%) had increased corticotrophin blood levels. These 11 patients, when scrutinised for subclinical pre-eclamptic toxæmia, were found to be quite normal, the other 44 women being just as normal. In 12 cases of toxæmia, 6 (50%) were found to have higher corticotrophin levels. Despite this difference we feel that the incidence of higher corticotrophin levels in toxæmia is not specific or pathognomonic. It may simply be the result of stress.[11]

The examination of 17-hydroxycorticoids in toxæmia of pregnancy also yielded inconsistent results. Some women had an excretion of up to 40 mg. per day, especially when corticotrophin levels were high, but about 50% of the cases had normal hydroxycorticoid values. On the other hand we encountered 3 normal pregnancies where these values were up to 30 mg. per day.

The excretion of 17-ketosteroids in 10 cases of toxæmia of pregnancy was found to be normal, sometimes even lower than that found in normal pregnancies.

Recently, Kumar et al.[12] found that in normal pregnancy there is usually a high aldosterone excretion with low intracellular sodium; and in pre-eclampsia the opposite.

Our results resemble those of Martin and Mills,[13] who studied aldosterone excretion in toxæmia of pregnancy. Finding inconsistent results, they came to the conclusion that " toxæmia of pregnancy is probably due to disturbance of the balance between all the sodium-retaining substances and all the sodium-excreting substances. There may be more than one cause for toxæmia."

Toxæmia of pregnancy was connected with increased corticotrophin production in only about half the cases. Excretion of 17-hydroxycorticoids was also increased in about 50% of cases, but low values were found just as frequently. Excretion of 17-ketosteroids was within the range of normal values.

If Browne's theory is correct, it can apply only to some cases of toxæmia. For the remainder another ætiology must be sought.

Department of Obstetrics and Gynæcology, Hebrew University-Hadassah, Rothschild Hospital. A. BRZEZINSKI Z. KOREN.

Department of Applied Pharmacology, Hebrew University-Hadassah Medical School and School of Pharmacy, Jerusalem, Israel. F. G. SULMAN.

AUTOIMMUNITY AND PERNICIOUS ANÆMIA

SIR,—In his article of Aug. 15 dealing with the inhibition of intrinsic factor by pernicious anæmia sera, Dr. Taylor refers to the possibility that some form of auto-immunity may play a part in the production of the disease.

We are carrying out investigations along these lines and during the past two years, in collaboration with Dr. Laureen Raine, I have examined a number of sera from patients with pernicious anæmia. We have used a modified Boyden's technique as applied to the detection of thyroid antibodies.[14 15] The antigen has been an extract of human gastric mucosa obtained from the fundus area.

In some sera, the results have been highly suggestive but the titres have never been as high as those obtained with thyroid antibodies. A number of sera, however, have proved negative. This may be due to the fact that our antigen requires further concentration and therefore the competition for the red-cell surface has been too widespread amongst the gastric mucosal proteins present in our extract.

The results of the tanned-red-cell technique are often difficult to interpret and we have been withholding publication until our own results become more clear cut. We are hoping to achieve this by further concentration and also by cell fractionation in the ultracentrifuge.

Department of Pathology, King's College and Royal Victoria Infirmary, Newcastle upon Tyne. A. L. LATNER.

EDWARD LAWRIE AND SIR GERALD BOMFORD

Dr. W. STANLEY SYKES writes:

" I am anxious to have a portrait of Edward Lawrie, born 1846, who died at Hove in 1915. He was residency-surgeon at Hyderabad. Also of Surgeon-Major Bomford, afterwards Sir Gerald Bomford, who took part in the Chloroform Commission. He was born in 1851 and died in 1915. If anyone can lend me either, or both, of these, they will be photographed and returned. My address is Glenholme, Morley, near Leeds."

1. Browne, F. J. *Lancet*, 1958, i, 115.
2. Sulman, F. G. *ibid.* 1952, i, 1161.
3. Sulman, F. G. *Acta endocr., Copenhagen*, 1954, **15**, 193.
4. Sulman, F. G. *ibid.* 1956, **22**, 107.
5. Cohen, H., Kleinberg, W. *Lancet*, 1952, ii, 201.
6. Sulman, F. G., Bergmann, F. *J. Obstet. Gynæc. Brit. Emp.* 1953, **60**, 123.
7. Assali, N. S., Hamermesz, J., Ross, M. *Endocrinology*, 1954, **55**, 561.
8. Gemzell, C. A. *J. clin. Endocrin.* 1953, **13**, 898; *Nord. Med.* 1956, **56**, 991.
9. Bayliss, R. I. S., Browne, J. C. M., Round, B. P., Steinbeck, A. W. *Lancet*, 1955, i, 62.
10. Bromberg, R. M., Sadowsky, A., Sulman, F. G. *Harefuah*, 1953, **45**, 146.
11. Sulman, F. G. *J. clin. Endocrin.* 1956, **16**, 755.
12. Kumar, D., Feltham, L. A. W., Gornall, A. G. *Lancet*, 1959, i, 541.
13. Martin, J. D., Mills, I. H. *Brit. med. J.* 1956, ii, 571.
14. Roitt, I. M., Doniach, D. *Lancet*, 1958, ii, 1027.
15. Witebsky, E., Rose, N. R. *J. Immunol.* 1956, **76**, 408.

Obituary

HAROLD ALBERT KISCH

M.B. Lond., F.R.C.S.

Mr. Kisch, whose death in London on July 31 at the age of 78 we announced last week, had been senior surgeon to the ear, nose, and throat department of University College Hospital for many years when he retired in 1946.

He came from a line of doctors, all associated with London. His father, Dr. Albert Kisch, was for many years a general practitioner in Sunderland Avenue and his grandfather an obstetric surgeon in Finsbury Circus. Educated at the City of London School, Harold Kisch went on to St. Thomas's Hospital where he qualified in 1904. After holding the appointments of house-surgeon and casualty officer at St. Thomas's he took the M.B. in 1906. Continuing his studies in surgery he became F.R.C.S. in 1911. During the 1914–18 war he served with the British Red Cross Society and later with the R.A.M.C., much of his service being spent in the Eastern Mediterranean and Salonika.

Early in his career as an ear, nose, and throat surgeon he became associated with the old Royal Ear Hospital then in Dean Street, Soho. In 1919 when this hospital amalgamated with University College Hospital and in 1927 moved into the Duveen Memorial Building as its E.N.T. department, he became a member of the staff of the teaching hospital. He was senior surgeon to the department from 1933 until 1946. As assistant surgeon and then surgeon to the Central London Throat, Nose, and Ear Hospital (now the Royal National Throat, Nose and Ear Hospital), and as dean of its postgraduate medical school, Kisch also took an important part in postgraduate teaching.

M. L. F. writes:

"With a thorough training in the principles and a good experience in the practice of general surgery, Harold Kisch was well equipped to take his place among the leaders in the relatively new specialty of otolaryngology. His frankness, clarity of expression, and intolerance for the idle enabled him to convey his point to the student in a manner that was both impressive and helpful. Beneath a somewhat rugged exterior there was a kindness of heart and gentleness of purpose which endeared him to all who knew him well. He was universally popular with patients, students, or staff, and at all times he had a word of sympathy or encouragement wherever one was deserved. His great interest and enjoyment in life was the individual, whether humble or exalted was of no consequence, and his approach was invariably accompanied by an irresistible cheerfulness. Although his contributions to otolaryngology were wide and varied, he will always be best remembered for personal characteristics, his help to his juniors and his generosity to those in need."

He was married in 1919 to Sybil Hyman, who survives him. There were no children of the marriage.

WILLIAM WILLOUGHBY FRANCIS

A.B., M.D. Johns Hopkins

Dr. Francis, librarian of the Osler Library at McGill University since its opening in 1929, died in Montreal on Aug. 10. He will long be remembered by students of medical history for his helpfulness and his erudition, but his most lasting memorial will be the *Bibliotheca Osleriana*, the magnificent catalogue of his kinsman's library.

He was born in Montreal in 1878, but a year or so later the family moved to Toronto where he grew up with his five brothers and three sisters. Their mother was a first cousin of William Osler who regarded the children as his nephews and nieces. Francis graduated from Johns Hopkins University, where Osler was now professor of medicine, in arts in 1898 and in medicine in 1902. He spent some years in Europe, doing postgraduate work in London, Berlin, Vienna, and Paris. In 1906 he returned to Montreal to practise as a physician. He was also a demonstrator in pathology at McGill University. In 1907 a pleural effusion, followed by apical pulmonary tuberculosis, forced him to give up practice, but 18 months of sanatorium treatment arrested the disease. From 1912–15 he was assistant editor of the *Canadian Medical Association Journal* and secretary-treasurer of the Association. In the 1914–18 war he served as registrar to No. 3 Canadian General Hospital (McGill) in France from 1915, and later spent nearly two years with the League of Red Cross Societies as editor of the *International Journal of Public Health*. When this journal ceased publication, he came to Oxford, in fulfilment of Osler's last wishes, to compile the *Bibliotheca Osleriana*. In this task he was helped by R. H. Hill, Archibald Malloch, and Leonard Mackall. Francis also gave much help to Harvey Cushing in writing Osler's biography.

In 1929 he crossed the Atlantic with Osler's books to preside over them at McGill. He wrote some excellent papers on medical history and biography, but his main task was to perpetuate Osler's memory, to preserve the Osler tradition of good will and scholarship. His many friends presented him with a volume of tributes in 1956, and he was elected an honorary fellow of the Royal Society of Medicine in the same year.

A. S. MacN., who shared rooms with him in London in 1906, writes:

"Bill Francis bore a close family resemblance to Sir William Osler in features, in dark eyes flashing with humour, in olive complexion, in stature, and gesture. He had no idea of time, was at his best between midnight and 2 A.M., and 'often tired the sun with talking' though never his audience. He had a dreamy air, a friendly smile, and played and sang French songs and Scottish ballads with much charm. When he was engaged on the *Bibliotheca* we used to meet either in London or Oxford, and after he went to Canada we kept in touch. In 1939 I spent a week with him in Montreal, and I heard from him only last month. He was happy in his home life, and he kept the spirit of youth and laughter to the end."

In 1921 Dr. Francis married Hilda Colley, who survives him with his daughter, Dr. Marian Kelen.

JAMES SHARPE

M.B. Glasg., F.R.F.P.S., D.P.H.

Dr. James Sharpe, who died on Aug. 5, had practised in Sheffield for nearly 20 years.

Born at Closeburn, Dumfries, 62 years ago, he was educated at the Wallace Hall Academy and at Glasgow University. After qualifying in 1924 he held house-appointments before he became deputy medical superintendent of the County Hospital, Motherwell, and clinical assistant at the Western Infirmary, Glasgow. In 1934 he moved to Leeds as deputy medical officer of health, and was honorary examiner in public health at Leeds University. He settled in general practice in Sheffield in 1940, and in 1948 he was elected the first chairman of the Sheffield local medical committee. He was known to many generations of students as medical officer to the Sheffield Rehabilitation and Training Centre.

A colleague writes:

"James possessed a remarkable capacity and appetite for work. A zealous family doctor, he somehow found time for a wide variety of additional duties and interests, and his enthusiasm and industry were in no way diminished by a coronary occlusion in 1953. A man of unusual kindliness and generosity, he will long be remembered with affection and gratitude by the many friends—of all ages—who enjoyed his hospitality, both in his home and at gatherings of the Sheffield Caledonian Society, of which he was president in 1950–51. His quiet courtesy was reminiscent of a more gracious era."

Dr. Sharpe leaves a widow and a son.

Notes and News

THE INJURED MINER

THE National Coal Board has built a model coal face in the grounds of the Astley Ainslie Hospital in Edinburgh. The Astley Ainslie is a convalescent home and rehabilitation centre which serves an area where there are about 14,000 miners, and last year 139 injured miners passed through it. In opening the model, Mr. Parker, chairman of the Scottish division of the N.C.B., reminded the visitors that coalmining is still a dangerous occupation; each year one in four of the miners in Scotland has an accident serious enough to keep him from work for at least 3 days.

The model consists of a short area of girdered roadway which leads into two seams, one 4 ft. 6 in. and the other 3 ft. 6 in. Actual mining conditions have been realistically reproduced with a travelling hutch and all the miner's usual tools: there are timber and stones for constructing roof supports. The model will certainly enable the injured miner to test himself thoroughly before going underground again. Its use will be supervised by the occupational-therapy staff of the hospital, many of whom have been underground and watched the work at the coal face.

The hospital and the National Coal Board are to be congratulated on a sensible and ingenious innovation.

THE FIRST X-RAY BURN

IT is well known that very many of the pioneers in the discovery and use of X rays and gamma rays died of skin cancer or blood diseases attributed to radiation; but one of them, thought to be the first person ever to sustain an X-ray burn, is still alive.[1] Beginning his career in the 1890s, as an assayer, Emil Grubbe discovered a deposit of platinum and went into the vacuum-tube business. During experiments with a tube he sustained a mysterious burn on his arm—in the summer of 1895, just before Röntgen's discovery of X rays was published. Grubbe later qualified in medicine and devoted himself to research, practice, and teaching in Chicago. Though still alive at 84, Dr. Grubbe has suffered much for his fellows, for he has lost parts of his face and both upper limbs, and has lately survived his ninety-second operation for cancer.

FILM FOR DIABETICS

A NEW film, *Living with Diabetes* (16 mm., sound, colour, 25 minutes, Britain, 1959),[2] is intended for showing to patients in whom the condition has been diagnosed.

Quoting the motto of the British Diabetic Association, " Balance is Life ", it states that a diabetic's special interest is in his diet and his pancreas: the balance between sugar and insulin is shown on a diagram. A dietitian interviews a large man and a slim woman and discusses their diets with them. Insulin is prescribed for the woman; and she discusses her fears with a doctor, who shows her how to prepare and give herself injections, and how to test her urine.

Finally the cause and symptoms of low and high blood-sugar levels are shown, and the commentator suggests that people should not put up with diabetes but should learn to live with it.

This film is suitable for the intended audience, though some of the demonstrations, such as of the insulin syringe, are too rapid. The accuracy and wisdom of the statement that fat diabetics need only to diet, whereas slim people need insulin is questionable, and the perfunctory dismissal of oral hypoglycæmic agents is unjustified. The quality of the picture and sound are below the standard previously established by this film unit.

University of Cambridge

Dr. Leon Radzinowicz, director of the department of criminal science, has been appointed to the new Wolfson professorship of criminology. Last April the Isaac Wolfson Foundation gave a grant of £150,000 to found a chair and a readership in this subject at Cambridge.

1. *Boston Globe*, July 24.
2. Obtainable free of charge from the Wellcome Film Library, 183-193, Euston Road, London, N.W.1.

Royal College of Physicians of Edinburgh

Queen Elizabeth, the Queen Mother, who was elected an honorary fellow in 1953, will dine privately with the president and fellows at the college on Saturday, Nov. 7. Afterwards she will sign the roll of fellows and have the fellowship conferred.

Harveian Society of London

Buckston Browne Prize.—The subject chosen for the next competition for this prize is Iatrogenic Disease. The prize is open to any doctor registered in Britain or the Dominions who is under 45 years of age. Essays must be sent by Aug. 31, 1960, to the hon. secretaries of the society, 11, Chandos Street, W.1.

Lister Lecture

Dr. N. B. Eddy, chief of the section on analgesics, National Institute of Health, Maryland, is to give this lecture on Thursday, Oct. 1, in Edinburgh. He will speak on chemical structure and action of morphine-like analgesics and related substances.

Postgraduate Medical School

Dr. E. H. Belcher will give a course of ten lectures on radioisotopes in clinical medicine and research on Tuesday afternoons from Oct. 13, and Dr. T. Alper, Dr. M. Ebert, and Dr. R. H. Thomlinson will give a course of six lectures on the biological effects of radiation on Thursday afternoons from Nov. 5. All the lectures will be given at 4 P.M. in the medical school, Ducane Road, London, W.12. Further particulars may be had from the secretary of the medical school.

Middlesex Hospital

On Thursday, Sept. 3, at 5.15 P.M. in this hospital, London, W.1, Prof. A. Gorman Hills, from the University of Miami School of Medicine, will give a lecture on some aspects of adrenal deficiency.

Institute of Diseases of the Chest, London

Clinical demonstrations will be continued at the institute (in the grounds of Brompton Hospital, Fulham Road, S.W.3) on Fridays, at 5 P.M., during September.

Chest and Heart Association

This association will hold a symposium on chronic bronchitis, on Sunday, Sept. 27, at 9.45 A.M. at Ashludie Chest Hospital, Monifieth. Tickets (10*s*.) may be had from the association, 65, Castle Street, Edinburgh, 2.

Nutrition and the Eye

The Nutrition Society will hold a symposium on this subject at Guy's Hospital Medical School, London, S.E.1, on Saturday, Oct. 10, at 10.30 A.M. Further particulars may be had from Miss D. F. Hollingsworth, c/o Ministry of Agriculture, Fisheries, and Food, Great Westminster House, Horseferry Road, S.W.1.

Hand Surgery

The Hand Club and the Second Hand Club will hold an open meeting at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2, at 10 A.M. on Saturday, Nov. 28. Dr. Erik Moberg of Gothenburg will be among the speakers. Further details may be had from Mr. H. Graham Stack, 150, Harley Street, W.1.

Inhaled Particles and Vapours

A symposium on this subject, arranged by the British Occupational Hygiene Society, will be held from March 29 to April 1, 1960, in Oxford. Further particulars may be had from Dr. J. S. McLintock, Medical Service, National Coal Board, Hobart House, London, S.W.1.

Increase in Poliomyelitis in U.S.A.

The United States Public Health Service reports that the week before last there was an increase of 33% in the weekly number of reported cases of paralytic poliomyelitis in the U.S.A. (*New York Times*, Aug. 15). The total of 245 was the highest weekly figure since September, 1956. This year's total stands at 1560, compared with 668 in the same period of 1958 and 3045 in 1955.

Institute of Child Health, London

Dr. J. A. Black has been appointed senior lecturer in child health, and Mr. James Lister senior lecturer in pædiatric surgery.

Working Party on Special Hospitals

The membership of this Working Party has now been completed by the appointment of Dr. D. H. H. Thomas, medical superintendent of Cell Barnes Hospital.

New Building for W.H.O.

Fifteen architects from 13 countries are to take part in a competition for the design of the new headquarters building of the World Health Organisation to be erected in Geneva.

Ministry of Agriculture, Fisheries, and Food

Dr. H. R. Barnell has been appointed as the Ministry's chief scientific adviser (food) in succession to Dr. Norman Wright who joined the Food and Agriculture Organisation of the United Nations last February.

Refugees

The Government have accepted in principle the proposals of the general committee of the World Refugee Year, including one for the admission of 150 refugees comprising both families and single persons, some of whom may require treatment or supervision for tuberculous infection.

Groupe International d'Études de la Trichomonase Humaine

This group has been set up under the auspices of the International Union Against the Venereal Diseases and the Treponematoses. The president of the group is Dr. Pierre Durel. Further particulars may be had from GIETH, Institut Alfred Fournier, 25, Boulevard St. Jacques, Paris XIVe.

Outpatient Appointments

A scheme to help doctors to save their patients from long waits in clinics is being tried in Liverpool. The Regional Hospital Board is supplying the office of the local executive council with information about the situation at each outpatient clinic, and this information is passed on by telephone to any doctor who inquires.

Ambulance Command Post

An ambulance bus has been converted for the London Ambulance Service into a command post which can be sent immediately to any major accident. It will be in charge of an officer who will control all ambulance work on the spot. From his command post the officer will be in touch with four sets of walkie-talkie apparatus which will be deployed at the scene under his direction.

A Journal of Veterinary Research

Under the editorship of Prof. D. L. Hughes, Dr. J. B. Brooksby, and Mr. H. E. Harbour, the British Veterinary Association is to publish a new quarterly journal, to be called *Research in Veterinary Science*. It will be published by Blackwells of Oxford, and the first issue will appear in January. Contributions should go to the Scientific Editor, 7, Mansfield Street, London, W.1.

Carlsberg-Wellcome Travelling Research Fellowships

The Carlsberg Foundation (Copenhagen) and the Wellcome Trust (London) announce a third series of awards of these fellowships, which they jointly instituted in 1957.

The successful candidates for 1959–60 are Mr. Michael Weis Bentzon, head of the statistical department of the State Serum Institute, Copenhagen, and Mr. J. A. Hunt, at present working in the Medical Research Council's Research Unit for Molecular Biology at the Cavendish Laboratory, Cambridge. Mr. Bentzon will work with Prof. M. S. Bartlett at Manchester University on the application of modern statistical theory to biological problems and Mr. Hunt will study methods of protein chemistry with Prof. M. Ottesen at the Carlsberg Laboratory, Copenhagen.

Dr. D. J. Gordon-Smith has been appointed deputy medical director to the Central Council for Health Education.

Dr. Derek Price has been appointed as visiting professor of the history of science at Yale University for 1959–60.

Dr. W. P. Cockshott of University College Hospital, Ibadan, has received a grant for radiological research from the James Picker Foundation which acts with the cooperation of the National Academy of Sciences, 2101 Constitution Avenue, N.W. Washington, 25, D.C.

The Multiple Sclerosis Society have made the following grants for research: Newcastle Royal Infirmary, £9500; University of Leeds, £8100; University of Manchester, £1000.

The University of Rochester offers Buswell fellowships to graduates of approved medical schools who wish to pursue research in any of the departments of their school of medicine or dentistry. Further information may be had from the chairman, Committee on Buswell Fellowships, Department of Medicine, University of Rochester Medical Center, 260, Crittenden Boulevard, Rochester, 20, New York.

The league of friends of Hellingly Hospital are sponsoring a concert at Glyndebourne on Sunday, Sept. 27, at 3 P.M., by the London Mozart Players.

The autumn dinner of the Wessex Rahere Club will take place at the Lansdown Grove Hotel, Bath, on Saturday, Oct. 31. Membership of the club is open to all Bart's men practising in the West Country. The hon. secretary is Mr. A. Daunt Bateman, 11, The Circus, Bath.

CORRIGENDUM: *Plasma Fibrinolytic Activity in Pregnancy*.—This is the correct title of the paper by Professor Gillman and his colleagues in our issue of Aug. 1. We regret that it appeared incorrectly as Plasma Fibrinogen Activity in Pregnancy.

Appointments

ALLEN, W. H., M.B., B.SC. Wales, D.C.H., D.P.H.: deputy M.O.H. and deputy principal school M.O., East Ham.
BAILEY, A. G., M.B. Manc.: assistant M.O. (maternity and child welfare) and assistant school M.O., Leicester.
BUNTING, J. B., M.B. Cantab., D.O., D.O.M.S.: ophthalmologist, West Cornwall clinical area.
RATLIFF, A. H. C., M.B. Manc., F.R.C.S.: consultant orthopædic surgeon, Southend-on-Sea hospital group.
SIMPSON, G. W., M.B. Edin., D.P.H.: assistant M.O.H., West Lothian.
WENN, JOAN M., M.B. Lond.: assistant M.O.H. and school M.O., Newcastle-upon Tyne.

The Hospital for Sick Children, Great Ormond Street, London:

BETTIO, E., M.D.: resident officer to neurological and neurosurgical department.
BLOOM, V. R., B.M. Oxon.: house-physician.
CHAMBERLAIN, G. V. P., M.B. Lond., D.OBST.: house-surgeon.
ELDERKIN, F. M., M.B. Durh., D.C.H.: house-physician.
ELLIS, J. D., M.B. Cantab.: house-surgeon.
GUTHRIE, ELINOR J., M.B. W'srand: assistant R.M.O., Tadworth Court, Surrey.
HIERONS, C. D., M.B. Durh.: house-surgeon.
METTEN, ANNE C., M.B. Sheff., D.C.H.: house-physician.
TAYLOR, H. C. C., M.D. Lond.: house-physician.

London County Council:

BARNARD, MILDRED M. E., M.B. Lond., D.P.H.: M.O.
FRENKIEL, ANNA L., M.R.C.S., D.OBST.: M.O.
KERR, LILIAN, M.B. Glasg., D.P.H.: M.O.
MARTIN, C. R. A., M.B. Lond., D.P.H., D.I.H.: M.O.
POWER, NORA T. E., M.B., N.U.I., D.P.H.: M.O.
YOUNG, G. C., M.B. Wales, D.P.H.: M.O.

Newcastle Regional Hospital Board:

CLARK, J. S. G., F.R.C.S.E.: senior casualty officer, South-West Durham group of hospitals.
KEEN, R. I., M.B. Sheff., F.F.A.R.C.S., D.A.: consultant anæsthetist, Newcastle upon Tyne group of hospitals.
PRINSLEY, D. M., M.D. Durh., M.R.C.P.E.: consultant physician, North and South Tees-side groups of hospitals.
QUINN, P. J. G., M.R.C.P.I., D.P.M.: consultant psychiatrist and deputy medical superintendent, St. Nicholas Hospital, Gosforth.
SAUNDERS, H. G., M.B. Aberd., F.F.A.R.C.S.: consultant anæsthetist, North and South Tees-side groups of hospitals.
WALDIE, WILFRED, M.B. Glasg.: senior casualty officer, South Tees-side group of hospitals.
WHEELER, H. Q. O., L.R.C.P.E., F.F.A.R.C.S., D.A.: consultant anæsthetist, Sunderland group of hospitals.

Births, Marriages, and Deaths

BIRTHS

JAGO.—On Aug. 10, at the Radcliffe Infirmary, Oxford, to Dr. Margaret Jago, wife of Douglas Hewitt—a daughter, Victoria.

DEATHS

KISCH.—On July 31, Harold Kisch, F.R.C.S., beloved husband of Sybil and son of the late Albert Kisch, M.R.C.S., consulting surgeon to University College Hospital, National Throat, Nose, and Ear Hospital, and the London Jewish Hospital. The cremation (private) took place on Aug. 4.

SCOTT.—On Aug. 10, in Poole General Hospital, Margaret Linden, wife of Dr. John Burleigh Scott, of Studmore, Parkstone, Dorset.